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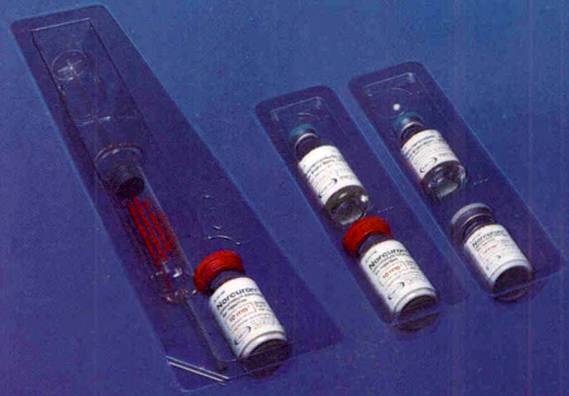

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Anesthesia and Analgesia

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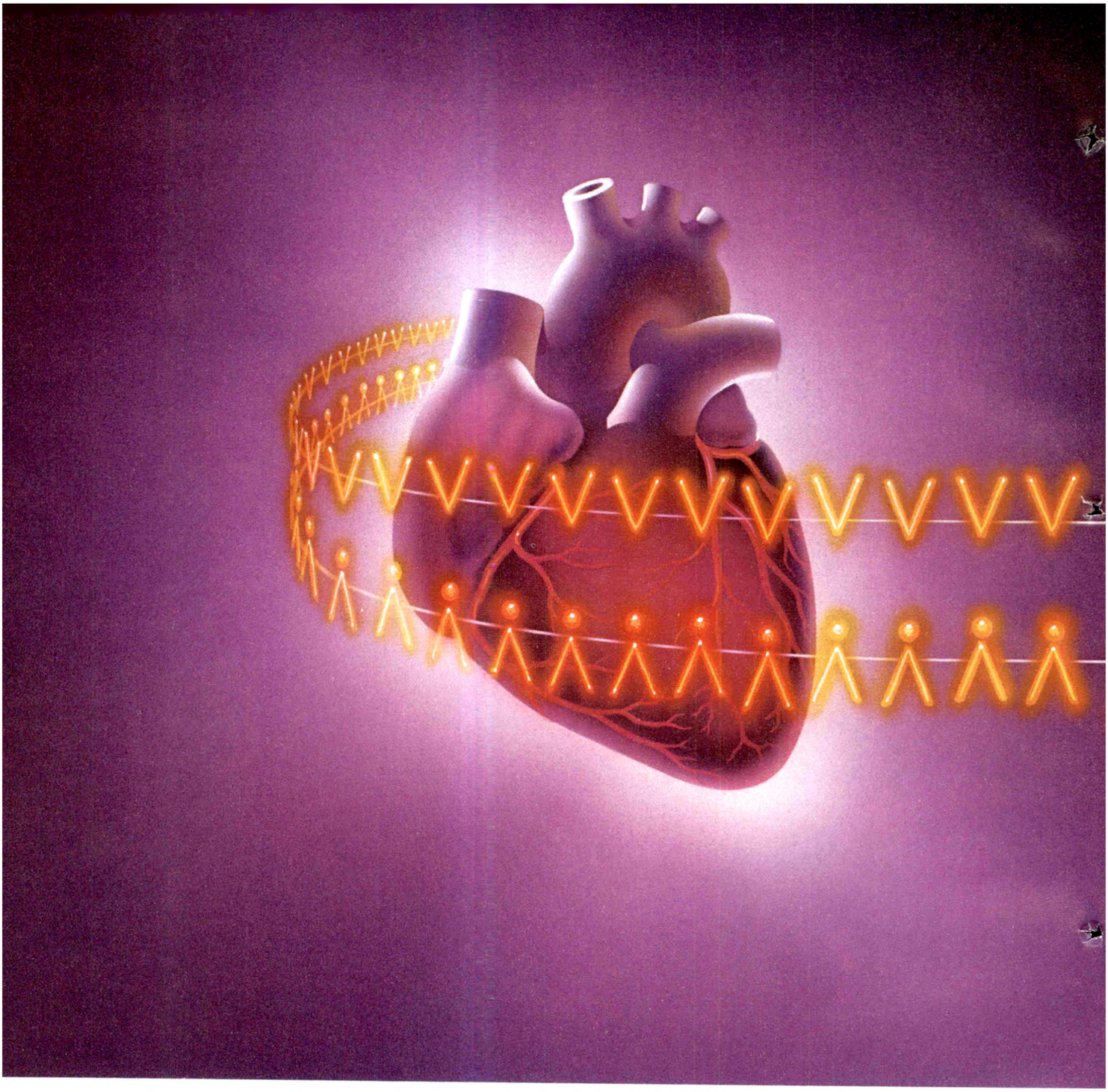

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Editorial

A Primer on "Grind and Bind"

D. R. Waud, MD, DPhil

Key Words: RECEPTOR—binding. IONS, CALCIUM—channels.

These days one frequently sees examples of studies of binding of some compound to some subcellular system. The general approach has become so common that it has picked up a nickname—"Grind and Bind" (some would say "Grind, Bind, and Find"). On the other hand, the details are not mainstream material for a medical curriculum so most physicians have only a vague notion of what exactly is going on. This strikes me as inappropriate. Scientific literacy requires enough acquaintance with the tools of the trade to be able to read papers based on common techniques. This issue of the journal contains an example (1) of a paper in the "grind and bind" category, so I shall take this opportunity to try to put the general approach into context. I shall operate on the assumption that either the reader is rather rusty when it comes to chemical kinetics and the like or that the reader, like myself, may have been in medical school before many of these ideas saw the light of day. In other words, I shall try to spell things out. The more sophisticated reader can skim, skip the whole discussion, or sulk.

My intent is to walk you through the highlights of the art of "grind and bind" and then, with the general picture still fresh in mind, walk through the paper of Blanck et al. to illustrate what one looks for in such a paper.

The Context

The setting is the reaction of some compound with some site in the body. That is the general case but, to be less vague, let us work in the specific setting of the paper at hand and imagine binding of the drug nitrendipine—a "calcium channel blocker" to some site on a calcium channel.

(The experts can find various types of calcium channel so generally extra adjectives have to accompany that "calcium channel." The calcium channel of particular interest, that in cardiac muscle, has "voltage-dependent" added to its name to distinguish it from others by noting that its behavior depends on the voltage gradient in which it finds itself. We don't care about that feature in the current context so we'll drop the extra verbal baggage to maintain focus.)

Binding of the sort we shall be considering is then represented schematically by something along the lines of

$$N + R \rightleftharpoons NR$$

where N refers to the drug, nitrendipine, and R to the binding site or receptor.

(That "or receptor" brings up another frill we'll ignore. Binding of drugs to enzymes, receptors or plasma proteins is similar although the end result can be considerably different [breaking of bonds, triggering of a signal, just sitting there, respectively]. Since we are focusing on the first step—interaction of the drug with whatever site it is going to tickle—most of the discussion will apply to any of these three general cases. However, again for simplicity, I shall phrase things in the setting of the nitrendipine binding reaction in heart and leave it to the reader to remember that we could just as well be talking about many other analogous systems, for example, binding of dopamine to some site in the central nervous system.)

Now, the picture

$$N + R \rightleftharpoons NR$$

implies a reaction of two compounds with each other and this, in turn, implies the reaction can be characterized by a binding constant. I'll choose the dissociation constant since biologists tend to lean that way, and write its definition:

Received from the Department of Pharmacology, University of Massachusetts Medical School, Worcester, Massachusetts.

$$K_d = \frac{[N]\cdot[R]}{[NR]} \quad (1)$$

(where the square brackets, as usual, imply concentration, for example [N] = concentration of N).

That scheme

$$N + R \rightleftharpoons NR \quad (2)$$

also implies a finite amount of receptor, R. One can express this feature more explicitly by saying

$$[R]_{total} = [R]_{free} + [NR] \quad (2)$$

in other words, the binding site is either free or occupied by drug.

These equations, 1 and 2, represent a formal description of the system, but one that is not convenient. Generally, one is interested in the relation of the concentration of bound drug, [NR], to the free concentration, [N], (for example, because the bound form leads to the effect we are trying to produce while the free form represents the plasma level we try to achieve to induce that effect). Thus, the first equation is usually plugged into the second to eliminate [R] (we had two equations in two unknowns and this is the unknown of lesser interest to us) and the result is rearranged to give what we are interested in, [NR], as a function of what we try to adjust, [N]. The result is

$$[NR] = [R]_{total}\frac{[N]}{[N] + K_d} \quad (3)$$

(if you have never gone through this derivation, get a piece of paper and give it a try—it's a useful educational exercise).

Now I want to change symbols, both to match convention in binding studies, and because the new ones will be easier to remember. The total concentration of receptors, $[R]_{total}$, becomes B_{max} (as in maximal possible extent of binding) while the concentration of bound drug, which equals [NR], becomes B. Finally, the concentration of free drug, [N], becomes simply F. In this setting our binding equation becomes

$$B = B_{max}\frac{[F]}{[F] + K_d} \quad (3')$$

a somewhat tidier form.

So what do we have so far? We have an explicit quantitative description of binding of drug to some site. In particular, we see that there are two parameters involved, B_{max} and K_d. This means that we have to know two numbers if we want to characterize any given binding site.

I'll be coming back to use these results later, but I'll shift away from the mathematics for a spell to allow the hypersensitive reader a breather.

Grind

Now let's turn to the real world. Picture a test tube with a rat's heart in it and imagine you want to examine binding of our drug, nifedipine, to calcium channels in that organ.

It doesn't take much thought to recognize that the tissue in our test tube is heterogenous. It contains potentially many sites that might react with our drug. If we were to try to study binding in the whole organ we might reasonably expect to get a complex picture which would be hard, if not impossible, to interpret. Such considerations lead us to try to separate the calcium channels from the rest of the heart.

Delving deeply into the "how" of the separation could get us into technical details (and often some black art) which are generally of interest only to those who want actually to do such a separation. All we need here is a general picture.

The method tends to follow a rather simple pattern. One reduces the heart to a mush and then tries to throw away everything but the part with the binding site of interest.

The standard way to begin is to grind the tissue in a homogenizer ("grind"). It helps to have a mental picture of what this does. If you picture the starting material as some sort of three-dimensional analog of those cells you saw back in your histology course, the grinding will turn this into a mixture of membrane fragments, mitochondria, nuclei, chunks of the contractile apparatus, and so on.

Next one tries to purify. Simply spinning the sample in a centrifuge will separate the more dense from the less dense components. If your interest is in one of the former, you keep the pellet, while if something still floating is the focus, you keep the supernatant. You can now try a second stage to purify further. One might, for example, make what is called a density gradient. This is a centrifuge tube filled with, for example, a sucrose solution which increases in concentration of sugar as you go deeper. If you then lay your sample on the top and spin the tube, the heavy components will fall to the bottom, the light ones will stay on top, and those of intermediate size will form a band in the middle. With some trial and error, you may be able to arrange to have your fragments of interest do the latter so as to give you a reasonably pure band in one step. This approach can be quite powerful. For example, one can fish out from heart the fragments corresponding to noradrenergic sympathetic nerve endings. When one realizes that these nerve endings represent an extremely small part of the heart as a whole, it is easy to see how impressive gradient techniques can be in separations. Now I have glossed over a key issue.

How does one know what is in any given fraction or how does one locate a fractionation which will do the desired job? Again, we are into details of principal interest to the specialist, but I shall try to give a general idea of the approach. Consider the nerve endings I just mentioned. One could try a sucrose gradient and assay various levels for norepinephrine. If the gradient was a good choice, one such fraction would contain a large amount of the transmitter and you would think you were on the right track. Next, you could get a colleague with an electron microscope to look at a sample of the material in that fraction to see if there are little bags of membrane surrounding granules with the "dense cores" seen in the original nerve ending. Similarly, if you were looking for mitochondria, you would look for the characteristic cristae in the electron microscopic picture.

Suppose you were interested in mitochondria, but did not want any surface membrane clouding the picture. Simply seeing the cristae tells you that you have the mitochondria, but this does not mean there is no contamination with surface membrane. How could you estimate the extent of that? One general approach is to find an enzyme which exists only on the surface membrane and see if you can find its activity in your "mitochondrial" fraction. Since enzymes can be quite active, you can turn this into a respectably sensitive test. This can all sound fine until you ask yourself "How do I find out whether an enzyme exists only on the surface membrane?" The trick here is to use a histological assay for the enzyme to show that it appears in a microscopic section only at the place where the cell membrane lies.

The foregoing comments are intended only to give the general impression that, although a lot of trial and error work coupled with imaginative reasoning may be involved, in principle it is a relatively straight forward process to isolate a reasonably pure preparation of many cell structures.

Bind

Now that we have a fraction which we feel is pure enough, we can go on to the next step—examining its properties. The ability to react with relevant drugs is often high on the list, not just because it is there to be done but because it can serve as a "probe" of the structure of the entity of interest. Remember that we started with an intact heart. We turned it into a purplish-brown soup, threw away most and kept either a small bit of white material ("pellet") in the bottom of a centrifuge tube or a small volume of a clear, colorless liquid from the supernatant. In either case, looking at what we have in our hand is not very informative. We therefore resort to poking it. One way to do so is to see how tightly it binds to a drug. This can immediately be useful two ways. If the dissociation constant matches that found in vivo, one tends to feel the isolation has not been too violent. Secondly, by comparing binding affinity before and after some intervention, one can see whether the intervention affects the binding site (this is the strategy in the paper we are presently interested in).

Because the details of the mechanics do not interest us, I shall outline the general approach, we shall imagine our cell fraction of interest was the one that ended up in the pellet in the bottom of the centrifuge tube (this is in line with Blanck et al.). We can now take this material, resuspend it, put aliquots in a series of test tubes, and add a radioactive drug in a series of concentrations to each tube. The drug will bind to the sites in the little bits of membrane fragment floating in the solution so that some drug becomes bound while the rest remains free. We now have to find out how much is in each state. This means we have to separate the bound drug from whatever is still free.

A general approach is to filter the solution through an appropriate sieve so that the bound drug ends up on the filter while the free drugs percolates through to the vessel below. We can then put the filter in a radioactive counting apparatus to determine the amount bound. We can subtract to determine the free amount because we know how much we added in the first place. Alternatively (especially if we like internal checks), we can count the liquid that came through the filter and make sure everything adds up (if it doesn't, the drug may have bound to the test tube wall, for example). We can also include appropriate controls such as making sure the drug does not bind to the filter.

It is unlikely that any cell fraction you get after a few purification steps will contain only one thing. For example, if you are isolating membrane fragments to get calcium channels, you'll have a lot of other structures that live in membranes as well as the membrane itself. It is thus rather naïve to expect to see binding to only one site. In fact, you may have your compound follow the membrane fragments onto the filter disk not because of binding but simply because the compound is lipid-soluble and membranes contain lots of lipoidal regions. Membranes also contain many charged sites so ligands with charges can be trapped nonspecifically as well.

The simplest solution to this problem involves the use of some nonradioactive drug to compete with the radioactive drug for the binding sites of interest. Since the chance of both drugs binding to irrelevant sites should be small, you should not be able to

displace radioactive drug from these irrelevant sites. Similarly, if there is a contribution to uptake onto the membrane fragments from simple solution into the membranes, this should not be altered by the second drug. Thus, in the presence of the second drug you will see "nonspecific binding"—everything but the binding that interests you. If we now subtract that level of binding from the ("total") binding we see in the absence of the competing agent, the difference will be what we want—"specific binding."

That's the general idea. The situation can be a little more complicated but we'll postpone that problem until later. For the time being we'll assume we have corrected the raw binding values for nonspecific binding and are now looking at just "specific binding" (where those quotes remind us to stay on guard).

Interpret

At this point, we have a set of paired values of F and B. Now we have to see what information is there.

In general, a binding assay takes place in the setting of equation 3'. One tries to determine whether the binding is in accordance with that relationship and, if so, what the values of the two parameters B_{max} and K_d are. We shall look at these two steps in turn.

Shape. If the binding is in accord with the simplest model, then a plot of B vs F will take on a specific shape—that given by equation 3'. The top panel of Graph 1 shows that shape. I simply plugged a few values of F (relative to K_d) into equation 3' to get some reference points and then drew a curve through them. It is clear that the relationship is not a straight line. The eye cannot easily tell us which of many possible nonlinear curves we might have. Biochemists have addressed this problem by converting the format of the plot to one that is a straight line. The eye can then tell much more easily if the shape is respectably consistent with the model.

There are several ways to do this linearization. The lower panel of graph 1 shows one—the "Scatchard plot." (I have sinned in drawing the graph—I omitted the scales on the two axes. I did this to avoid distractions; I wanted simply to focus on the shape.)

It is easy to show that this format should be a straight line. If we start with equation 3' and cross multiply to clear out the denominator on the right we get

$$B \cdot F + B \cdot K_d = B_{max} \cdot F \qquad (4)$$

Now, if we divide through by $F \cdot K_d$ we get equation 5:

$$\frac{1}{K_d} B + \frac{B}{F} = \frac{B_{max}}{K_d} \qquad (5)$$

which can be rearranged into the form $y = a + bx$ of a straight line as seen in equation G:

$$\frac{B}{F} = \frac{B_{max}}{K_d} - \frac{1}{K_d} B \qquad (6)$$

which tells that, if we plot B/F against B, we will get a straight line with a y-intercept of B_{max}/K_d and a slope of minus (i.e. the line will go down and to the right) $1/K_d$. Nowadays one can automate this determination of linearity with a computer (and do it in a more sophisticated manner while you are at it) but I'll leave the reader with the Scatchard plot both because it is simpler and because it is frequently encountered.

So now we take our values of B and F from the binding assay, plot them, and see if we get a linear Scatchard plot. If we do, we can conclude that everything is consistent with equation '3 and go on to the next step of parameter estimation. If not, we have trouble. There are many reasons the plot could be curved. One obvious one is that we have two "specific" binding sites. If so, one can consider either working some more on the purification procedure or telling one's computer to sort it out. In any case we (but not everyone) would be reluctant to try to go much further. A curved plot has an aura of "back to the drawing board" about it. Whenever I encounter a "grind and bind" paper, one of the first things I look at is the shape of the binding curve. If it wiggles too much, I tend to tune out.

Parameter Estimation. If the binding seems to be in line with equation 3', then we can go ahead and get estimates for the parameters B_{max} and K_d.

I introduced the Scatchard plot to make the present job easy. We can simply look at the plot and the intercept with the *B-axis* gives us B_{max} while the negative of the inverse of the slope gives us K_d. There are more sophisticated ways to extract specific numbers but we need not explore that avenue. Suffice it to say one can pull the numbers out easily.

Function

As you may suspect from the preceeding comments, it may often not be possible to demonstrate function in these subcellular fractions. For example, the function of a calcium channel is to let cacium ions cross the cell membrane. However, in a preparation of membrane fragments, it is not easy to look at flow of ions through the channel. Thus there can be some uncertainty as to what exactly you have in your preparation. You can demonstrate binding, but not function.

Ultimately one can get a rigorous demonstration. One follows the biochemist's yellow brick road of isolate, characterize, synthetize, and reconstitute. Once you have the material in a pure form, you can put it back into the membrane of a cell (Xenopus eggs are a favorite target, as are artificial lipid bags called liposomes; the former are popular when you want the cell to use its synthetic machinery to make the compound for you, the latter if you want the simplest preparation) which does not normally demonstrate the activity in question and then show that now it does.

By the time you can do this you are well along in your study. What do you do until you reach that point? There is no clear answer. You have to walk the tightrope between a quick-and-dirty approach that will almost certainly let you down, and an overly compulsive approach that, while never misleading, is so slow you are left behind by the rest of the world. There is considerable art to reaching the most effective middle-of-the-road position.

In any case, to avoid getting misled, it is a very good idea to keep firmly in mind the fact that the assay measures binding not function.

A Test Run

Now let's take that guided tour through the paper of Blanck et al.

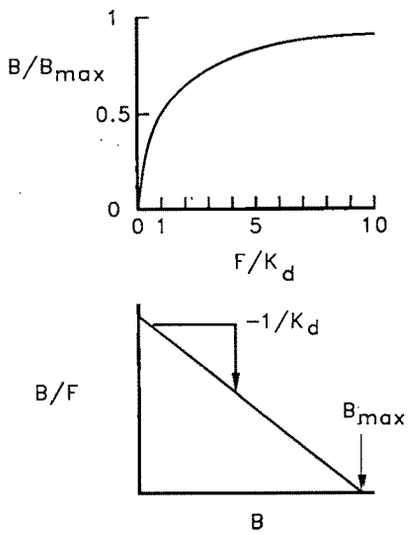
I start at the title. First I pick out the word "binding" and then look for reagents. I see "calcium antagonist" and "cardiac membranes" and already have a good idea of where we are going. I don't expect halothane to bind to anything, so I suspect it will be perturbing the binding system.

The first paragraph of the introduction tells me that we are going to use the binding assay as a probe. We suspect halothane tweaks the calcium channel. If the binding of a drug which reacts with that structure is altered then we are going to say the halothane alters the channel.

The next paragraph tells us that the probe will be a radioactive form of nitrendipine, a compound known to interfere with function of calcium channels.

The first paragraph of the methods section tells us amateurs more than we really want to know so we skim. Basically it appears nasty things are done to a rat heart with the result a pellet of a membrane fraction which is supposed to contain calcium channels. The next paragraph tells us rabbits fare no better. We don't care about such details as "50% maximum speed" or ' "Tissumizer" ' (although the latter sounds ominous—especially from the point of view of the rat); we'll assume the authors can pull it off.

In the next paragraph we see that the study is beginning to fit the pattern we expect. The terms



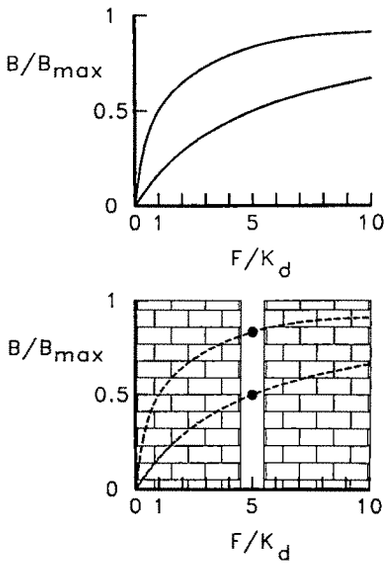
Graph 1. Sketches to indicate the shape of the relationship given by equation. Top, the "straight up" plot. The dependent variable, B, is plotted as ordinate against the independent variable, F, as abscissa. The relationship is clearly curved. Bottom: The Scatchard plot. The variable B/F is plotted against B. Now the graph becomes a straight line. The slope can be used to estimate K_d, while B_{max} can be read off from the intercept with the horizontal axis. As B increases, you travel out to the right horizontally, down and to the right along the straight line. when you go as far as you can, you must be at B_{max}. Scales are purposely omitted (see p. 1028).

"nonspecific" and "specific" are beginning to appear. We learn that nitrendipine can fall apart in the light and park that bit of information in the store we use for Trivial Pursuit.

The following paragraph brings up something we might not have anticipated. Apparently the authors are concerned that the observed effects be demonstrably reversible. On reflection, this seems an admirable goal, so we approve.

In the last paragraph of the methods we see the halothane concentrations. They bracket MAC so we know we shall not simply be looking at the effect of an organic solvent.

We are left with a slight sense of something missing. The term Scatchard does not arise. Nor is there any indication of some more sophisticated way to confirm the binding fits the model. We go back to look again and see that only one concentration of nitrendipine was used. What is going on? We have to assume that the authors chose not to do a full binding assay but rather to pick a point somewhere in the middle of the range of F and look just there. We presume this was a compromise associated with balancing labor and rigor. Trying to do just about any sort of experiment in the presence of a volatile anesthetic tends to be a tour de force so we can understand why one might try to streamline. Nevertheless, we make a mental note to come back to this issue.



Graph 2. Sketches to represent the likely effect of halothane and then to indicate the viewpoint associated with using only one concentration of ligand. Top: The top panel of Graph 1 with a second curve added to represent the relationship in the presence of halothane. Bottom: The same panel with blinders (brick walls) superimposed to indicate that, if you use only one concentration (F/K_d in this instance) of ligand, only one small section of the curves can be examined. In particular it is impossible to determine what happens overall to the shape of the relationship.

Now we go on to look at the results. The first paragraph directs us to their Figure 1. Now that plot, amount of ligand bound against concentration of halothane, is not what we expected. It doesn't look like either panel in graph 1 so we have to pause to put it into context. First we see two curves. However, we are told they represent "total" and "nonspecific" binding so we can mentally subtract the latter from the former to get what interests us. This amounts to seeing how much daylight there is between the curves. If we had the full binding curves we could expect something like the picture in the top panel of Graph 1, but there would be two curves on it, the control curve, and one in the presence of halothane. We suspect from the way things are heading that we'd have something like the top panel of Graph 2—the halothane curve is going to lie below and/or to the right of the control curve. The restriction of the assay to only one value of F means we are looking at things through a narrow window, somewhat along the lines of the sketch in the lower panel of Graph 2.

Now we can go back to look at Figure 1. We interpret it to mean that, had we done a series of full assays, the halothane curve would have fallen more and more down and/or to the right as the anesthetic concentration was increased. We also note in passing that the nonspecific binding was unaffected by halothane. This latter observation, while not earth-shaking, does suggest the halothane does not simply affect everything in sight; the drug is selective.

The next paragraph and Figure 2 tell us that bunnies behave like rats. It looks like the phenomenon is not peculiar to just one species and therefore is likely to extend to people.

Since Figures 1 and 2 are closely related we now go back and look at them together. We note a discrepancy. In Figure 1, the maximal depression of specific binding is to about 10% to 20% of control. In Figure 2 it is only to about 40% to 50%. We note, however, that Figure 1 purports to be a "typical" experiment and are familiar enough with human nature to suspect it was actually one which showed some of the more marked effects. However, let's follow that up and see if it's consistent with results. In looking at Figure 2, note that the sample size is about 18 for the rats and that the error bars are standard errors we can deduce that the original standard deviation was about $\sqrt{18}$, or slightly over four times larger. Recalling that two standard deviations should include about all the points, we conclude that Figure 1 was one of the best. We also note there must have been some in which halothane did not do very much.

Finally the table indicates the effect is reversible (a good thing).

At this point, we do not go on immediately to read the discussion. We ponder what we have so far before we give the authors a chance to brainwash us.

It looks like halothane reduces the binding of the nitrendipine to the membrane fragments (and does so reversibly). But we do not have full binding curves. Is there any caveat embedded in that lack? Obviously we shall not be able to tell whether the halothane affected B_{max} or K_d or both. But do we really care? If we just want to know whether halothane alters the channel we do not. A change in either B_{max} or in K_d implies the channel is altered. So we ask whether there is any way the points in Figure 2 could go down without implying a change in channel properties, in other words, whether the restriction of having to look through that window in the bottom half on Graph 2 could be hiding something.

If K_d were increased (halothane reduces binding affinity) the points would fall. If B_{max} were reduced (halothane reduces the number of binding sites) the points would also fall. So everything looks reasonable. We might have one slight remaining reservation. A reduction in K_d is easy to understand. Halothane dissolves in some nonpolar part of the channel structure (or associated membrane) and thereby distorts the structure so that the drug fits less readily. One can readily imagine this progressing in a graded fashion as the halothane concentration rises. When we turn to B_{max} things get slightly more awkward. A drop in B_{max} implies we have fewer binding sites. But this should go in steps of one binding site. In other words it is

hard to picture binding to half a binding site. We thus would have to conclude that, when we consider any single channel, introduction of a critical amount of halothane causes the structure to snap from one form that binds drug to one that does not. That would be very interesting kinetics. We begin to wish we had that Scatchard plot. Another issue merits consideration. How do we know that what we have in that pellet is the same thing that we look at when we study calcium conductances in an intact cell? One thing to look for is a respectable affinity of binding in the in vitro preparation. We look back at the methods section and see that they used 1 nM nitrendipine. That's a low concentration, so it appears that we are looking at a structure that does bind the drug tightly.

The choice of competing agent deserves attention. Nifedipine was used in rats, nitrendipine in rabbits. Which is a better choice when the radioactive ligand is nitrendipine? Intuition tends to mislead here; nifedipine wins. The reason is simply that, if the competing drug is the same as the radioactive one, all you should be able to rule out would be uptake (into membrane fragments), which does not involve reaction with some binding site (simple solution in the membrane is the paradigm). If there is any binding site involved and the radioactive version "sees" it, the cold version must see it equally well since they are chemically the same compound. (The only exceptions would involve either an "isotope effect"—the two forms do not behave the same way chemically, but then the use of the radioactive form becomes suspect; or binding so nonspecific as to have a huge K_d, in which case even the "large" concentration of cold compound might not be high enough to compete appreciably.) This is why I put quotation marks around that "nonspecific" and "specific" earlier. With nitrendipine as the competing agent, all binding will come out "specific". In my mind, I tend to replace "specific" with "displaceable"—a term that "tells it like it is" and is less likely to mislead me.

In the present context, therefore, we are relieved to see that at least one of the animals was done with some agent other than nitrendipine. A devil's advocate could still argue that we now haven't ruled out the combination of the halothane effect being on a nonspecific site in one species so that, in turn, the argument that the effect applies to all species becomes weaker. Most people, however, will not lose much sleep over that one.

Now we can read the discussion to see what the authors think. The first paragraph indicates they are concerned that the pellet is not pure—specifically, that it might contain calcium binding sites from other than the surface membrane which they would like to think they are studying. They argue reasonably that an occasional bit of contamination from sarcoplasmic reticulum should not confuse the assay since a preparation that has large amounts of that material shows no inclination to react with our drug nifedipine.

In the second paragraph they try to convince us that they have strengthened the argument that halothane reduces contractile force by altering the behavior of calcium channels. I admit that I did not see this position with quite the clarity the authors seem to experience. Given that halothane reduces the slow current at the plateau of the action potential, I find it hard to imagine how halothane could do this without affecting the calcium channel (the calcium concentration gradient does not change significantly so what else could cause the current fall?). Thus, the new results did not strike me as remarkable.

The last paragraph caught my eye when the authors mentioned that halothane but not enflurane nor isoflurane affect nitrendipine binding. I was not aware of much difference in the effects of these three agents on cardiac contractile force. My memory is atrocious so I took a peek at Goodman and Gilman (seventh edition) and on page 283, under enflurane, found "in vitro preparations of myocardium show dose-dependent, reversible depression of contractility . . . similar to that caused by halothane at equivalent doses." So I end up wondering whether the authors have not shot themselves in the foot. If enflurane depresses force but does not affect binding, does this not argue rather strongly that binding is irrelevant to the genesis of the reduction in force?

The last sentence seems to come out of left field. How one can deduce much about mechanism of anesthesia from what goes on in heart eludes me. I chalk that sort of sentence up to fatigue after writing the rest of the paper.

So where are we? We see a "grind and bind" type of study. Halothane seems to reduce binding of nitrendipine to the membrane fragments (although we should have liked to have seen a couple of Scatchard plots). In turn, we are inclined to accept the author's argument that this binding does indeed reflect what would occur at the calcium channels on the surface membrane of an intact cell. We do wonder, however, how to reconcile the hint about no effect of enflurane with the overlying thesis that halothane's negative inotropic action is a corollary of a depressant effect on those calcium channels.

References

1. Blanck TJJ, Runge S, Stevenson RL. Halothane decreases calcium channel antagonist binding to cardiac membranes. Anesth Analg 1988;67:1032–5.

Halothane Decreases Calcium Channel Antagonist Binding to Cardiac Membranes

Thomas J. J. Blanck, MD, PhD, Susan Runge, MD, and Robert L. Stevenson, MD

BLANCK TJJ, RUNGE S, STEVENSON RL. Halothane decreases calcium channel antagonist binding to cardiac membranes. Anesth Analg 1988;67:1032–5.

The effect of halothane concentration on the binding of the calcium antagonist, [^{3}H] nitrendipine (^{3}HNTP), to rat and rabbit heart membranes was examined in vitro because it has been hypothesized that one mechanism by which halothane depresses cardiac contractility is by interfering with Ca^{2+} channel function. Membranes were incubated for 30 minutes in a closed system with ^{3}HNTP and increasing concentrations of halothane. The amount of ^{3}HNTP bound to membranes was quantified by radioligand binding technique and liquid scintillation counting. It was found in both the rat and rabbit cardiac membranes that halothane (0.4–2.0%) caused a dose-dependent decrease in specific ^{3}HNTP binding ($P < 0.0001$). The decrease in ^{3}HNTP binding caused by halothane was also found to be reversible. These results indicate that halothane interferes with one property of the Ca^{2+} channel and suggest that this may be one possible mechanism for the negative inotropic action of halothane.

Key Words: ANESTHETICS, VOLATILE—halothane. HEART—contractility. HEART, CALCIUM CHANNEL BLOCKERS—nitrendipine.

One mechanism by which volatile anesthetics (VA) are believed to depress cardiac contractility is by interference with calcium homeostasis in the myocardial cell. Several sites within the cell, including the sarcoplasmic reticulum (SR), the myofibrillar proteins, and the sarcolemma, are involved in the transport and recognition of Ca^{2+}. Studies have demonstrated that the sarcoplasmic reticulum (1) the myofibrillar proteins (2-4), and the sarcolemma (5,7) can be modified by VA. The plateau phase of the action potential of ventricular muscle, which reflects the movement of Ca^{2+} through voltage-dependent channels of the sarcolemma, is depressed by halothane (5). Recently Bosnjak and Kampine demonstrated by aequorin luminescence that halothane decreases intracellular free calcium in papillary muscle during contraction, presumably by inhibiting Ca^{2+} influx into the cell (6). The above evidence suggests that halothane might decrease the influx of calcium by altering the calcium channels in the heart. In this study, we used the radioligand binding technique to examine this possibility.

To determine whether or not halothane alters one particular Ca^{2+} channel characteristic, we tested the effect of halothane on the binding of [^{3}H] nitrendipine (^{3}HNTP), a competitive voltage-dependent Ca^{2+} channel antagonist. Binding of ^{3}HNTP was used to quantitate one property of the Ca^{2+} channels. Any change observed in the amount of ^{3}HNTP binding, therefore, reflects an alteration in one property of the Ca^{2+} channel. Experiments were performed in two species, the rat and rabbit, because in both halothane is a myocardial depressant. Calcium channels have been widely studied in rat membranes, and most of our previous experiments into the mechanism of anesthetic depression were performed using rabbit hearts.

Methods

Sprague-Dawley rats were killed by cervical dislocation and decapitation. Hearts were removed, minced, and placed in 50-mM Tris HCL buffer at pH 7.7. The entire preparation was carried out on ice. The minced hearts were homogenized at 50% maximum speed for 45 seconds in a Tekmar "Tissumizer." The homoge-

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nate was filtered through cheesecloth and centrifuged at 1000 *g* for 5 minutes at 2°C. The supernatant was centrifuged at 39,000 *g* for 10 minutes. The pellet was resuspended in 25 ml 0.8M KCl to dissolve myofibrillary proteins, homogenized with a Dounce homogenizer, and allowed to stand on ice for 30 minutes. This suspension was centrifuged at 39,000 *g* for 20 minutes. The pellet was resuspended in 25 ml 50mM Tris HCl (pH 7.7) with a Dounce homogenizer and centrifuged at 39,000 *g* for 20 minutes. The pellet was washed three more times and was resuspended in Tris HCl buffer and frozen in liquid nitrogen (8).

Rabbits were anesthetized by IV injection of sodium pentobarbital (160 mg/kg) and their hearts were removed. Rabbit cardiac membranes were prepared by a modification (1) of the method of Harigaya and Schwartz (9). 3HNTP (78.3 ci/mmol) was purchased from New England Nuclear. Nifedipine was a gift of Pfizer Laboratories, nitrendipine was a gift of Miles Laboratories, and halothane was a gift of Halocarbon Laboratories.

Nitrendipine binding experiments were performed in 31-ml glass vials sealed with plastic caps and Teflon liners to maintain constant anesthetic concentration. The reaction medium contained 1 nM (0.1 μCi) of ^{3}HNTP in 50 mM Tris HCL, pH 7.7 and 0.150 mg cardiac membranes. Buffer pH was adjusted to 7.7 at 25°C. Protein analysis of the cardiac membranes was performed by the method of Bradford (10). All incubations were performed at 25°C for 90 minutes in the dark to minimize the photochemical decomposition of nitrendipine. Spectra of nitrendipine and nifedipine in the reaction medium were obtained before and after 90-minute incubation at 25° and demonstrated no decrease in the absorbance due to either compound. The rat membranes were incubated in the presence or absence of 10^{-6} M nifedipine and the rabbit membranes in the presence or absence of 0.5×10^{-6} M nitrendipine to define nonspecific binding. The different competing agents, nifedipine and nitrendipine, were chosen because of current availability, but gave equivalent results. Nonspecific binding is defined as that binding of ^{3}HNTP which occurs in the presence of a high concentration of unlabelled ligand. Specific binding, which indicates binding to the voltage-dependent Ca^{2+} channel, is the difference between total binding and nonspecific binding. After the incubation, an 0.8-ml aliquot of the reaction mixture was added to a Whatman GF/C filter under a vacuum and rinsed three times with 10 ml cold buffer. The filter was placed in 5 ml scintillation fluid and counted with a Beckman LS 2800 scintillation counter. Counting efficiency was approximately 55%.

The decrease in ^{3}HNTP binding to cardiac membranes was proved to be reversible by the following experiment. Rabbit cardiac membranes were classified into four groups. The first group of samples (control 1) were incubated with ^{3}HNTP for 60 minutes in the presence and absence of cold NTP and specific binding quantified. The second group of samples were treated as control 1, except 1.99% halothane was included in the incubation. Group 3 samples (control 2) were incubated for 60 minutes at 25° in a sealed vial, the cap was removed for a further 30-minute incubation, and then, for a final 60 minutes, ^{3}HNTP was added to the incubation mixture. The reaction was terminated at this time and the amount of ^{3}HNTP specifically bound to membranes was quantified. The final group of samples (halothane pretreated) were treated as were the samples in control 2, except 1.99% halothane was included during the first 60 minutes of incubation. As in control 2 samples, the caps were removed, in this case the halothane vaporized. Samples were then exposed to ^{3}HNTP for 60 minutes, and specific binding of ^{3}HNTP quantified. Statistical comparisons between control and treated groups were made using the nonpaired *t*-test.

Halothane was added in liquid form with a Hamilton microliter syringe. The concentrations studied were 0.39, 0.66, 1.31, and 1.97 volume %. Halothane concentration was determined in the vapor phase by infrared spectroscopy as previously described (11).

Results

Figure 1 shows total and nonspecific binding of ^{3}HNTP to rat cardiac membranes plotted against the vapor phase halothane concentration for one typical experiment. Each data point is the mean of three observations, with the error bars indicating the standard deviation. The total binding of ^{3}HNTP is decreased by halothane in a dose-dependent fashion, but halothane has no effect on nonspecific binding. The results are similar for rabbit membranes.

The dependence of Ca^{2+} channel-specific ^{3}HNTP binding on vapor phase halothane concentration is shown in Figure 2 for the rat (closed symbols) and for the rabbit membranes (open symbols). The data are presented as percentage control, i.e., the ratio of ^{3}HNTP specifically bound at a particular halothane concentration to the mean ^{3}HNTP specifically bound in the absence of halothane, multiplied by 100. It is apparent that specific ^{3}HNTP binding decreases with increasing halothane concentration, and that the response of both membrane types to halothane was

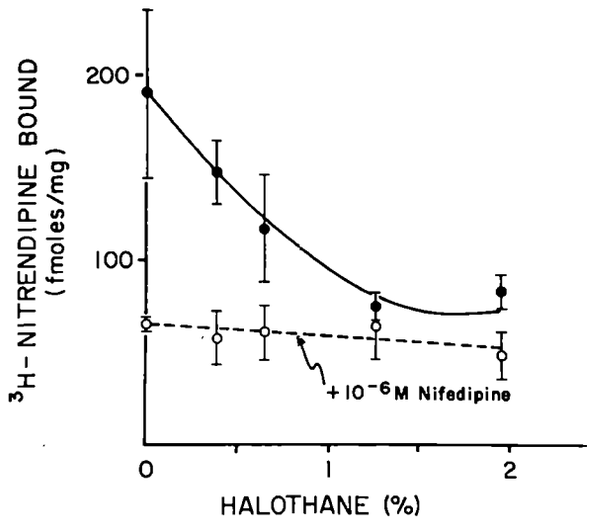

Figure 1. The binding of ^{3}HNTP to rat heart membranes as a function of halothane concentration. Incubations were performed at 25°C for 90 minutes. The incubation medium included 5 nM ^{3}HNTP in 50 mM Tris HCl at pH 7.7. Each point is the mean of three determinations; the error bars indicate the standard deviation. The upper curve indicates total binding, and the lower curve indicates nonspecific binding.

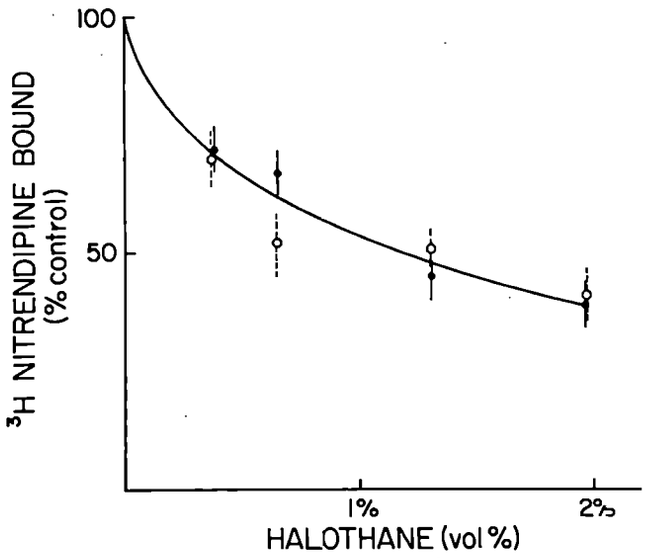

Figure 2. The amount of specifically bound ^{3}HNTP as a function of halothane concentration. Incubation conditions were as described in Figure 1. The data are expressed as percentage of control (0 halothane). Rat cardiac membranes (closed circles), each point is the mean of 18 experimental observations ± SEM and rabbit cardiac membranes (open circles), each point is the mean of nine experimental observations ± SEM.

essentially identical. The specific binding data were analyzed by a two-way analysis of variance, which demonstrated a statistically significant ($P<0.001$) inverse relation between specific ^{3}HNTP binding and halothane concentration for both rat and rabbit cardiac membranes.

Table 1. Reversibility of Halothane Inhibition of ^{3}HNTP Binding to Cardiac Membranes‡

	^{3}HNTP Bound (cpm)	% Control 1
Control 1	1158 ± 123	
Halothane	755 ± 122*	65
Control 2	1045 ± 116	90
Halothane-pretreated	1065 ± 113†	92

*$P < 0.05$ versus control 1.
†No significant difference from control 2.
‡Values are means ± SEM.

Table 1 demonstrates the reversibility of the halothane effect on the binding of ^{3}HNTP to rabbit cardiac membranes. During 60 minutes of halothane exposure, ^{3}HNTP binding was depressed by 35% relative to control 1 samples. After allowing the halothane to vaporize for 30 minutes, control and treated membranes demonstrated equivalent binding during a 60-minute incubation with ^{3}HNTP.

Discussion

The membrane preparation that we used contains elements from both the sarcolemma and the sarcoplasmic reticulum. The rat membrane preparation is one that has been used by other investigators to demonstrate Ca^{2+} channel antagonist binding sites (8). The rabbit membrane preparation was designed by Harigaya and Schwartz (9) for studies of cardiac sarcoplasmic reticulum, but was shown by Besch et al. to contain a significant amount of sarcolemma (13). At this time we have not established the relative proportion of sarcoplasmic reticulum to sarcolemma. Williams and Jones observed that not only the sarcolemma, but also the sarcoplasmic reticulum contains specific, high affinity Ca^{2+} channel antagonist binding sites (14). This observation has recently been clarified by Brandt, who demonstrated that cardiac SR does not contain nitrendipine binding sites, and that the SR binding of ^{3}HNTP demonstrated by William and Jones was due to contamination of SR membranes by tightly bound sarcolemma which could be dissociated with the detergent, digitonin (15). Furthermore, the ^{3}HNTP binding sites, previously thought to be associated with the SR, were functionally unrelated to SR Ca^{2+} uptake and release (16,17). Although our membrane preparations are impure, Brandt's paper indicates that our experiments are directed at Ca^{2+} antagonist binding sites on the sarcolemma, and that halothane is decreasing the specific binding of ^{3}HNTP to sarcolemmal voltage-dependent Ca^{2+} channels.

At this time little direct evidence is available to localize the negative inotropic effect of halothane to

one specific subcellular site. Lynch (5) demonstrated that the plateau phase of isoproterenol stimulated slow action potentials is decreased by halothane; this observation suggests that the movement of Ca^{2+} through the voltage-dependent Ca^{2+} channels is decreased by halothane. The voltage-dependent Ca^{2+} channels involved in the slow action potential are located in the sarcolemma and are the sites at which ^{3}HNTP specifically bind. Bosnjak and Kampine (6) showed by the use of Ca^{2+} sensitive aequorin luminescence that intracellular Ca^{2+} is decreased by halothane during papillary muscle contraction. They could not unequivocally attribute the decrease in intracellular Ca^{2+} to either decreased influx of Ca^{2+} through the SL Ca^{2+} channels or decreased release of Ca^{2+} from the SR. They noted that verapamil, a Ca^{2+} antagonist that binds to the voltage dependent Ca^{2+} channels, caused a marked decreased in intracellular Ca^{2+}. These observations, together with our observation that the specific binding of ^{3}HNTP to voltage dependent Ca^{2+} channels is decreased by halothane in a reversible manner, suggest that the sarcolemma is one of the important negative inotropic sites of action of halothane.

It has long been debated whether volatile anesthetics act by altering membrane structure due to their high lipid solubility or by specific actions on certain protein targets in the cell. Our data could be interpreted by invoking either mechanism, but the fact that halothane decreases specific binding of ^{3}HNTP, while in preliminary observations, enflurane and isoflurane have markedly less effect, suggests a direct effect of halothane on the Ca^{2+} channel antagonist binding sites (18). The decrease in ^{3}HNTP binding to membrane Ca^{2+} channel antagonist binding sites by halothane has implications not only for the mechanism of depression of cardiac contractility but also for the mechanism of general anesthesia in the central nervous system.

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Combined Depressant Effects of Diltiazem and Volatile Anesthetics on Contractility in Isolated Ventricular Myocardium

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LYNCH. Combined depressant effects of diltiazem and volatile anesthetics on contractility in isolated ventricular myocardium. Anesth Analg 1988;67:1036–46.

Because the volatile anesthetics depress the entry of calcium (Ca) into myocardial cells and also alter release of intracellular Ca stores, additional pharmacologic blockade of Ca entry could potentially enhance anesthetic-induced depression. The depressant effects of the calcium entry blocker diltiazem combined with the volatile anesthetics halothane, enflurane, or isoflurane were investigated in isolated guinea pig papillary muscle. Muscle contractions were studied in normal Tyrode solution after rest and at stimulation rates of 0.1, 0.25, 0.5, 1, 2, and 3 Hz. Anesthetics were studied in the presence of 0.1 and 1 μM diltiazem, which depressed tension to approximately 85 and 55% of control at 2–3 Hz, respectively; depression at the higher concentration was frequency-dependent. Depressant effects of enflurane were determined as previously done for equianesthetic concentrations (approximately 1 and 2 MAC) of halothane and isoflurane. At all stimulation rates, 1.7 and 3.5% enflurane depressed peak tension and dT/dt-max to approximately 73 and 50% of the mean control-recovery value, respectively. After control measurements of contractile characteristics, effects of 0.1 μM diltiazem were determined alone and then with the addition of halothane (0.75 or 1.5%), isoflurane (1.3 or 2.5%), or enflurane (1.7 or 3.5%), respectively. Recovery from anesthetic was then determined in the continued presence of diltiazem. After rest and at rates ≤ 0.5 Hz, equianesthetic concentrations of these volatile agents caused similar depression in the presence of diltiazem. At 3 Hz stimulation rate, 1.3% isoflurane caused significantly less contractile depression than did 1.7% enflurane or than 0.75% halothane. At 2-MAC concentrations, differences among the anesthetics were more apparent: 2.5% isoflurane depressed peak tension and dT/dt-max less than did halothane at 1–3 Hz stimulation rates, and depressed dT/dt-max less than 3.5% enflurane at 2–3 Hz. Similar frequency-dependent differences in depression by approximately 2 MAC anesthetics were observed in the presence of 1 μM diltiazem. The patterns of depressant action by the volatile anesthetics were similar to those previously observed in the absence of diltiazem. Furthermore, when the volatile anesthetic depression of contractions was combined with the depression due to diltiazem-induced blockade of Ca entry, the resulting contractile depression did not differ significantly from a prediction that assumed simply additive effects.

Key Words: ANESTHETICS, VOLATILE—enflurane, halothane, isoflurane. HEART, CONTRACTILITY—diltiazem. INTERACTIONS (DRUG)—diltiazem and anesthetics. IONS—CALCIUM—diltiazem. PHARMACOLOGY—diltiazem.

Diltiazem is a widely used calcium entry blocker employed in the treatment of coronary artery disease. By inhibiting Ca^{2+} entry into the cell, diltiazem depresses myocardial contractility and decreases vascular smooth muscle tone (1,2), which in turn reduces work of the heart, increases coronary blood flow, and thus improves the metabolic supply:demand ratio in the myocardium. Volatile anesthetics also appear to decrease Ca^{2+} entry into the cells (3–5) in addition to altering internal Ca^{2+} uptake and release in the myocyte (6–10), so that multiple mechanisms contribute to anesthetic depression of contractility. In whole animals, a dose-dependent depression of cardiovascular performance was observed with the combination of diltiazem with isoflurane, but without evidence of myocardial ischemia (11–14). Such studies are complicated by various considerations, including the presence or absence of baseline anesthetic, alteration in baroreceptor and sympathetic responses, and the presence of an open or closed chest in the experimental model. Nevertheless, the weight of evidence had led to the suggestion that combinations of calcium entry blockers and anesthetics may be

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safely employed and may indeed be of benefit in anesthetizing patients with coronary artery disease (15).

By causing additional Ca channel blockade and/or by interfering with subsequent steps in myocardial excitation-contraction coupling, the anesthetics may enhance the depressant action of diltiazem. Alternately, Ca^{2+} entry may already be depressed by diltiazem and the additional multiple actions of anesthetics upon contractile depression might become less apparent. Therefore, the depressant actions of halothane, isoflurane, or enflurane combined with the effects of diltiazem were examined in isolated myocardium, a model in which the confounding effects of reflex responses are eliminated.

Previous studies (5,10) in isolated guinea pig and rabbit papillary muscle have demonstrated that equianesthetic concentrations of halothane depress contractility more than does isoflurane at physiologic frequencies. Furthermore, halothane depresses the rate of depolarization of the slow action potential, a measure of Ca^{2+} current through the slow channel, more than does isoflurane. In light of such a difference, one might speculate that the depressant action of diltiazem, mediated by Ca^{2+} entry blockade, might be more enhanced by halothane than by isoflurane. Therefore, this study also examined whether the differences in myocardial depression among the volatile anesthetics are enhanced or masked in the presence of blockade of Ca^{2+} entry by diltiazem.

Methods

Isometric contractions of guinea pig papillary muscles from the right ventricle of guinea pigs (250–350 g) were studied as previously described (5). Briefly, papillary muscles were excised from the right ventricle, pinned by the cut end to the base of the chamber (volume = 3 ml), and superfused at 37 ± 0.5°C with Tyrode solution (composition in mM: Na, 143; K, 4.7; Cl, 128; Ca, 2.5; Mg, 2.0; SO_4, 2.0; HCO_3, 25; glucose, 11; EDTA, 0.1). Solution circulated through the chamber (8 ml/min) from heated reservoir containers through which 95% 0_2/5% CO_2 was bubbled, maintaining pH at 7.45 ± 0.5. Isometric tension development was measured by attaching the muscle tendon to a Grass FT03 force transducer or a Cambridge Technology Series 400A Force Transducer System. Muscle length was adjusted to the smallest resting tension at which maximum active tension developed. The muscles were field-stimulated with stimuli of 0.5–1 msec duration. Preparations were equilibrated for one hour in the chamber during constant stimulation at a rate of 0.5 to 1 Hz, with intermittent short periods of stimulation at 0.1 to 2 Hz to verify muscle integrity and define performance.

The following stimulation protocol was employed to determine the force-frequency relation for control, drug exposure, and recovery periods: after 10–15 minutes rest, a rested state (RS) contraction was elicited, followed by stimulation rates of 0.1, 0.25, 0.5, 1, 2, and 3 Hz. A rest period of at least 10 minutes was required to produce an unchanging rest response. These muscles demonstrated a typical "positive staircase," with increasing tension development as the frequency increased, especially above 0.5 Hz. With each increase in stimulation rate, tension development increased over 20 to 45 seconds to a stable and unchanging response. Each stimulation rate was maintained for at least 30 seconds or until such a steady-state and unchanging contraction was established and recorded, before proceeding to the following higher frequency. Stimulation at 2–3 Hz for more than 60–90 seconds caused peak tension to decline, probably caused by muscle fatigue and hypoxia in the core of the muscle; prolonged stimulation resulted in permanent deterioration in contractile performance. Brief periods (30–60 seconds) of stimulation at 2 and at 3 Hz achieve stable, reproducible peak developed tensions, and prevented subsequent deterioration of preparations' contractile pattern at each frequency during the 2- to 4-hour experiments.

Anesthetics were applied by passing the 95%O_2/5%CO_2 gas through calibrated vaporizers before bubbling through the reservoirs. When equilibrated with the gas phase, the superfusate solution at 37°C contained the following anesthetic concentrations measured by gas chromatography: 0.75 and 1.5% halothane gave 0.20 and 0.38 mM; 1.3 and 2.5% isoflurane gave 0.22 and 0.42 mM; 1.7 and 3.5% enflurane gave 0.40 and 0.76 mM.

The following pattern of drug application was used. Following control force-frequency determination, 0.1 μM diltiazem was applied to the muscle and the force-frequency response observed at 20–30 minutes; anesthetic was then applied and the force-frequency behavior observed after 20–30 minutes. Finally, the anesthetic was discontinued and the force-frequency relation again determined at 30–40 minutes, with typical recovery to 85–100% of the preanesthetic contractile behavior. In many of the studies employing isoflurane and halothane, one anesthetic was applied after recovery from the previous anesthetic (order randomized), permitting a paired study.

In contrast to the volatile anesthetics, discontinuation of diltiazem in pilot studies only occasionally resulted in recovery to within 90% or more of the control behavior, suggesting residual drug effect. Therefore, after its addition, 0.1 μM diltiazem was subsequently maintained throughout the course of the experiment, and recovery from diltiazem was not systematically examined.

The effects of the combination of diltiazem and the different anesthetics were compared by employing two separate analyses:

The first question addressed was: How does the experimentally observed combined depression compare with that predicted assuming a simple additive effect? If diltiazem and the anesthetic alter the tissue in such a way that each drug does not augment (or diminish) the action of the other, then at each frequency the effect of the drugs together may be expressed as the product of each individual effect, that is (equation 1):

$$\text{Predicted effect (\% control)} = [\text{diltiazem effect (\% control)}] \times [\text{anesthetic effect (\% control)}]/100.$$

For example, if diltiazem results in an 80% of control response, and the anesthetic response is 70% of control, one would predict that together they should produce a response that is 56% of control. Because the anesthetic and the diltiazem experiments were all performed in identical preparations, it is possible to quantitatively predict a response in this tissue assuming a simple additive effect according to equation 1. The significance of the difference between the predicted response and the observed response was tested by a single-sample *t*-test, employing the calculated prediction as the tested population mean.

The second question addressed was: Do the characteristic and different depressant effects of the anesthetics which have been previously observed (5,6,10) persist in the presence of diltiazem? For any group of muscles (n = 5 to 8) exposed to a given anesthetic concentration, the variation in the depression caused by the prior application of diltiazem alone could increase (or decrease) the observed differences among the anesthetics. That is, variation in the diltiazem effects among preparations might produce or mask differences between each diltiazem–anesthetic combination. Furthermore, if diltiazem caused any small additional depression after the 30-minute initial exposure, this could mistakenly be attributed to the anesthetic effect. The differing depression among the anesthetics in the presence of diltiazem could be more accurately compared by reducing the effects of time-dependent changes in contractility caused by the preparation itself or by late (≥ 30 minutes) effects of diltiazem. Therefore, the anesthetic effect on contractile characteristics (peak tension and dT/dt-max) at each frequency was expressed as a percentage of the average of the pre- and postanesthetic contractile characteristics in the presence of diltiazem (equation 2):

$$\text{Anesthetic effect (as \% control)} = \frac{\text{(response with diltiazem plus anesthetic)} \times 100\%}{0.5\ \text{(preanesthetic diltiazem response)} + 0.5\ \text{(postanesthetic diltiazem response)}}.$$

The significance of difference between the anesthetic values at each frequency was tested by ANOVA employing Duncan's multiple range test. Differences in depressant effects caused by enflurane alone or diltiazem alone at the different stimulation rates was also calculated employing an ANOVA and Duncan's multiple range test.

Results

Effects of Diltiazem on Contractility

Figure 1A shows the typical pattern of control tension responses observed after rest and at the stimulation rates studied. There is a clearly positive force–frequency relation that is typically observed in guinea pig papillary muscle. When the stimulation rate is increased and maintained, the developed tension increases to a new steady-state response at each higher rate, with greater peak developed tension and increased rate of tension development (dT/dt). With increasing stimulation rate, the duration of the contraction also decreases, and the pattern of tension development is altered. The responses at each frequency were depressed by 0.1 μM diltiazem to 80-90% of the control value; 1.0 μM diltiazem caused greater depression especially at 2–3 Hz, so that much of the positive force-frequency relation was lost. The effects on peak developed tension of 0.05 μM up to 10 μM diltiazem were observed in four muscles in which increasing diltiazem concentrations were sequentially applied. The dose dependence of contractile depression is shown (see Fig. 1B) for the rested state contractions and those at 3 Hz, and demonstrates the difference in depression observed at these extremes of stimulation rate. Rested state contractions were depressed by 17% for each ten-fold concentration change. Contractions at a rate of 3 Hz showed a

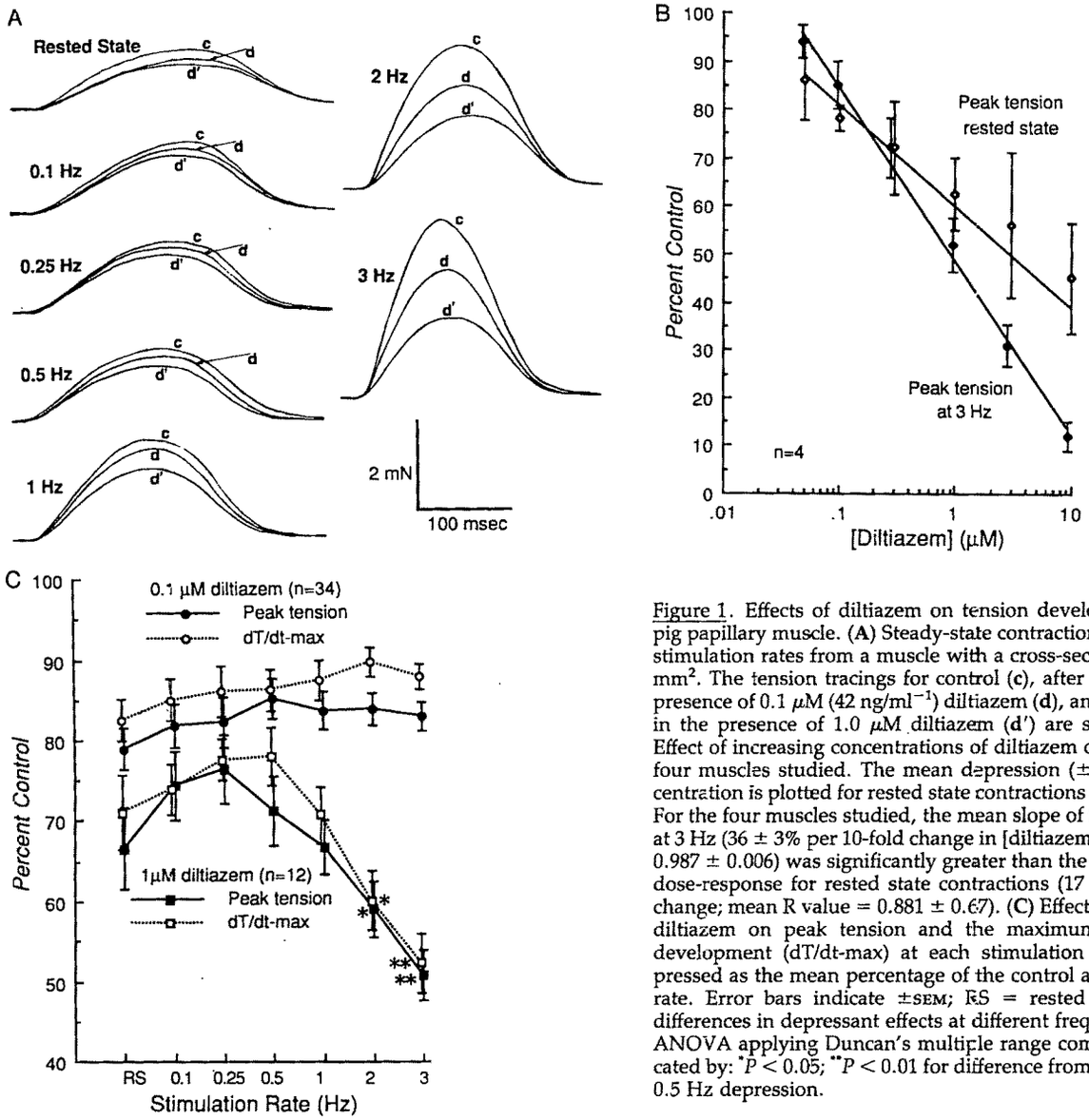


Figure 1. Effects of diltiazem on tension development in guinea pig papillary muscle. (**A**) Steady-state contractions at the indicated stimulation rates from a muscle with a cross-sectional area of 0.31 mm^2. The tension tracings for control (**c**), after 30 minutes in the presence of 0.1 μM (42 ng/ml^{-1}) diltiazem (**d**), and after 30 minutes in the presence of 1.0 μM diltiazem (**d'**) are superimposed. (**B**) Effect of increasing concentrations of diltiazem on peak tension in four muscles studied. The mean depression (±SEM) at each concentration is plotted for rested state contractions and those at 3 Hz. For the four muscles studied, the mean slope of the dose-response at 3 Hz (36 ± 3% per 10-fold change in [diltiazem]; mean R value = 0.987 ± 0.006) was significantly greater than the mean slope of the dose-response for rested state contractions (17 ± 3% per 10-fold change; mean R value = 0.881 ± 0.67). (**C**) Effect of 0.1 and 1.0 μM diltiazem on peak tension and the maximum rate of tension development (dT/dt-max) at each stimulation rate studied, expressed as the mean percentage of the control at each stimulation rate. Error bars indicate ±SEM; RS = rested state. Significant differences in depressant effects at different frequencies (tested by ANOVA applying Duncan's multiple range comparison) are indicated by: $^{*}P < 0.05$; $^{**}P < 0.01$ for difference from RS, 0.1, 0.25, and 0.5 Hz depression.

significantly steeper dose-dependent depression of peak tension, decreasing 36% for each ten-fold increase in diltiazem concentration. The dose dependent changes in the maximum rate of tension development (dT/dt-max) paralleled the changes in peak tension. Figure 1C shows the effect of 0.1 and 1 μM diltiazem on peak tension and dT/dt-max at each stimulation frequency. Diltiazem (0.1 μM) caused similar depression of peak tension and/or dT/dt-max at all heart rates, with depression to 83–89% of control at 2–3 Hz. In contrast, 1 μM diltiazem caused somewhat greater depression of contractions after rest up to 0.5 Hz, but much more marked depression of contractility as the stimulation rate was increased to 2–3 Hz.

Effects of Enflurane on Contractility

The effects on guinea pig papillary muscles of 1- and 2-MAC halothane and isoflurane with identical experimental conditions and stimulation rates have previously been reported (5). To appropriately analyze the combined effect of diltiazem and enflurane, it was necessary to first determine the effect of enflurane by itself. Figure 2 shows the mean contractile depression caused by 1.7 and 3.5% enflurane (approximately 1 and 2 MAC levels) after rest and up to stimulation rates of 3 Hz, with peak tension and dT/dt-max plotted as percent of average control and postanesthetic response. At the various stimulation rates, depression of peak tension was relatively uni-

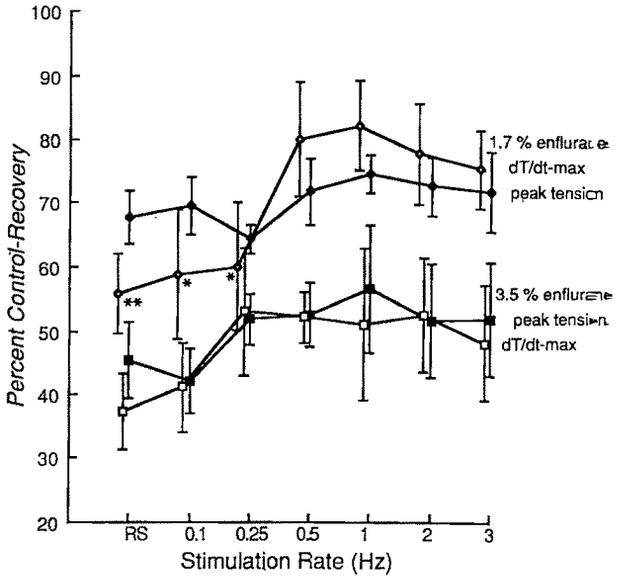


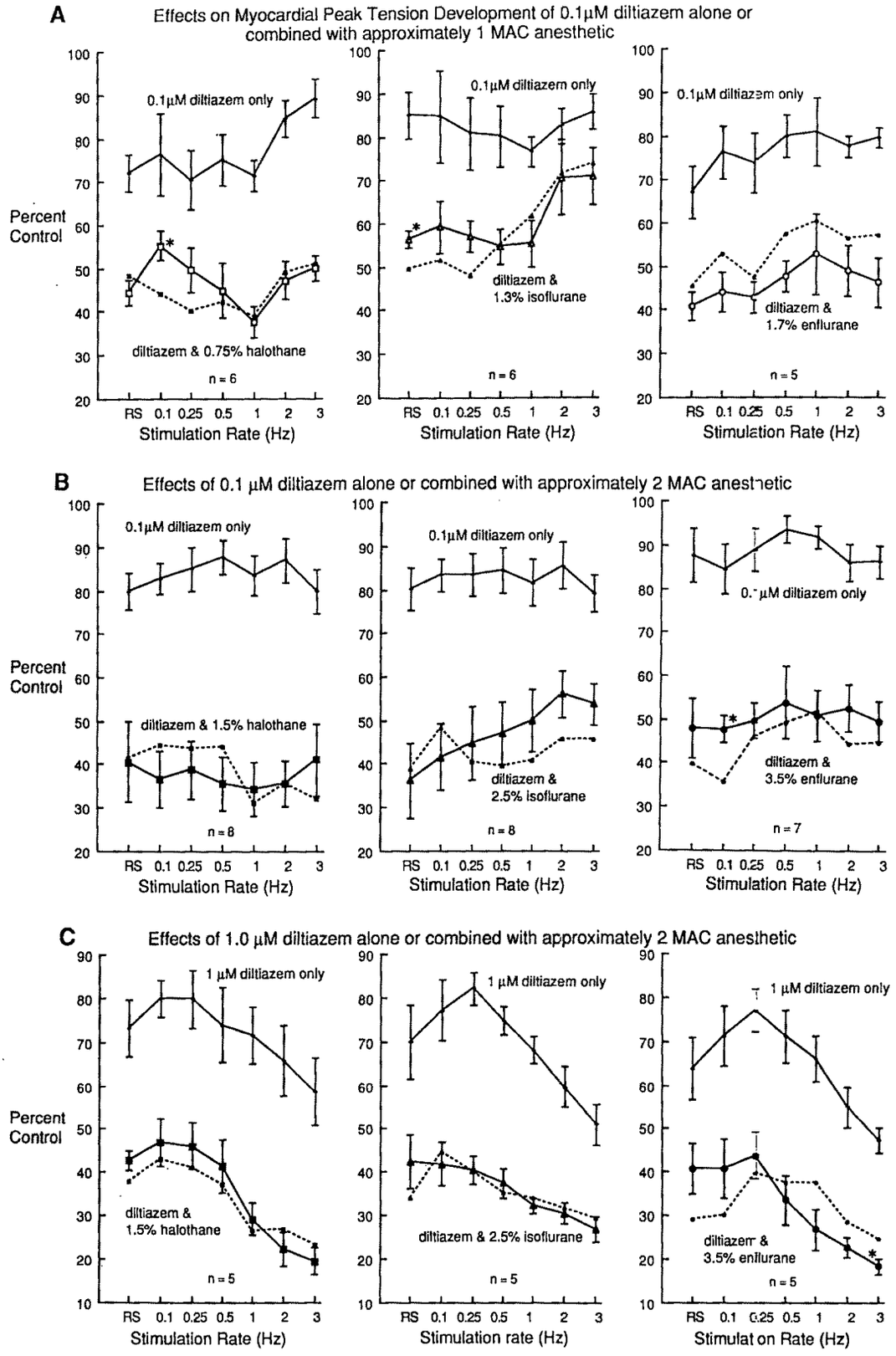
Figure 2. Effects of approximately 1 and 2 MAC enflurane at various stimulation rates on peak tension (1.7%, ◆; 3.5%, ■) and dT/dt-max (1.7%, ◇; 3.5%, □). The mean (±SEM) depression due to enflurane is plotted as a percent of the average of the control and recovery (post-anesthetic) values. **P<0.01 different from depression at 0.5–3 Hz. *P<0.05 different from depression at 1–3 Hz.

form. However, 1.7% enflurane did cause significantly less depression of dT/dt-max at 1–3 Hz stimulation than it did after rest and up to 0.25 Hz.

Effects of volatile anesthetics combined with diltiazem. Figure 3 plots the peak tension observed at each stimulation rate in the presence of drug(s) as a percentage of the control tension at that rate. The upper curve in each panel is the mean change observed 30 minutes after application of either 0.1 μM or 1.0 μM diltiazem. As previously noted, 1 μM diltiazem (Fig. 3C) showed a frequency-dependent depression of contractility at rates ≥ 1 Hz, an effect not observed with 0.1 μM diltiazem (Fig. 3A,B). For each stimulation rate, the diltiazem effect for each group of muscles (n = 5 to 8) and the known effect of the anesthetics (enflurane results above; halothane and isoflurane effects from Reference 5, Fig. 3) were used according to equation 1 to predict simple additive depression. Each prediction is depicted by the dashed line in each panel. Subsequent application of 1 MAC (Fig. 3A) or 2 MAC (Fig. 3B,C) anesthetic resulted in the observed mean depression indicated by the lower solid line in each plot. Significant difference (P <0.05) between the observed mean (±SEM) and predicted value for the combined drugs was rare (indicated by an asterisk), occurring in only 4 instances out of 63 comparisons (9 anesthetic/diltiazem combinations at 7 stimulation frequencies). Plots of the depression of dT/dt-max were similar in appearance to those for peak tension, and are not shown. Observed and predicted values of dT/dt-max were in good agreement, with only 5 significant differences occurring out of the 63 comparisons tested.

Figure 3. Change from control peak tension at each stimulation rate caused by diltiazem alone or in combination with approximately 1 and 2 MAC anesthetic. Plotted for each group of muscles is the mean effect of diltiazem alone (+): 0.1 μM in **A** and **B**, 1.0 μM in **C**. The subsequent mean depression 20–30 minutes after the addition of 0.75% halothane (□), 1.3% isoflurane (△), or 1.7% enflurane (○) is shown in **A**. The subsequent depression after addition of 1.5% halothane (■), 2.5% isoflurane (▲), or 3.5% enflurane (●) to 0.1 μM diltiazem is plotted in **B** and **C**, respectively. Error bars indicate the SEM. The dashed-line plots the predicted depression at each frequency due to diltiazem combined with anesthetic, assuming simple additive depression according to equation 1 (see text). The mean diltiazem effect for each group of muscles and the previously determined depression due to 1 or 2 MAC halothane or isoflurane (from Ref. 5), or enflurane (see Fig. 2) were employed in the prediction. *Indicates a significant difference ($P < 0.05$) between the observed effect at each frequency versus the calculated prediction, which was used as the hypothetical mean in a one-sample t-test.

As is apparent from Figure 3, the contractile depression at various frequencies due to diltiazem by itself was somewhat variable, especially at a concentration of 0.1 μM. This variation in depressant effect by diltiazem will necessarily combine with the subsequent anesthetic mediated depression. To more accurately assess the differences among anesthetics in the presence of diltiazem, anesthetic effects on peak tension and dT/dt-max at each stimulation rate were expressed as a percentage of the value in the presence of diltiazem alone (both pre- and postanesthetic) according to equation 2. Figure 4 plots the percentage depression of peak tension due to 1 and 2 MAC anesthetics in the presence of diltiazem. Isoflurane was the only anesthetic for which contractile depression varied with frequency: for 0.1 μM diltiazem, both 1 and 2 MAC concentrations of isoflurane caused significantly less depression of peak tension at 2 and 3 Hz (indicated by a dagger). With regard to differences among the anesthetics, isoflurane was significantly less depressant than halothane or enflurane as the preparations were stimulated at physiologic rates (2–3 Hz). At 3 Hz 1.3% isoflurane was less depressant than was 1.7% enflurane at 3 Hz. In a subset (n = 5) of experiments that paired 0.75% halothane and 1.3% isoflurane, halothane depressed peak tension significantly more than did isoflurane at 2–3 Hz, although no significance was present in the unpaired ANOVA (Fig. 4, left panel). The difference among the anesthetics was most apparent at 2 MAC in the presence of 0.1 μM diltiazem (Fig. 4, middle panel): 2.5% isoflurane caused less depression of peak tension than did 1.5% halothane at 1–3 Hz, while also being less depressant than 3.5% enflurane


A
Effects on Myocardial Peak Tension Development of 0.1μM diltiazem alone or combined with approximately 1 MAC anesthetic
Percent Control
0.1μM diltiazem only
diltiazem & 0.75% halothane
n = 6
0.1μM diltiazem only
diltiazem & 1.3% isoflurane
n = 6
0.1μM diltiazem only
diltiazem & 1.7% enflurane
n = 5
RS 0.1 0.25 0.5 1 2 3
Stimulation Rate (Hz)
B
Effects of 0.1 μM diltiazem alone or combined with approximately 2 MAC anesthetic
Percent Control
0.1μM diltiazem only
diltiazem & 1.5% halothane
n = 8
0.1μM diltiazem only
diltiazem & 2.5% isoflurane
n = 8
0.1μM diltiazem only
diltiazem & 3.5% enflurane
n = 7
RS 0.1 0.25 0.5 1 2 3
Stimulation Rate (Hz)
C
Effects of 1.0 μM diltiazem alone or combined with approximately 2 MAC anesthetic
Percent Control
1 μM diltiazem only
diltiazem & 1.5% halothane
n = 5
1 μM diltiazem only
diltiazem & 2.5% isoflurane
n = 5
1 μM diltiazem only
diltiazem & 3.5% enflurane
n = 5
RS 0.1 0.25 0.5 1 2 3
Stimulation Rate (Hz)

at 3 Hz. In the presence of 1 μM diltiazem, the differences in contractile depression by 2 MAC anesthetics were present, albeit less apparent (Fig. 4, left panel): In a subset of paired anesthetic exposures, 2.5% isoflurane was less depressant at physiologic rates (2–3 Hz) than was either 1.5% halothane ($n = 4$) and 3.5% enflurane ($n = 3$).

Similar effects with regard to both the sparing of depression at 2–3 Hz by isoflurane as well as the differences among the anesthetics were observed for dT/dt-max (data not shown). In the presence of 0.1 μM diltiazem: 1.3% isoflurane was less depressant than was 1.7% enflurane and 0.75% halothane at 3 Hz; 2.5% isoflurane depressed dT/dt-max less than did 1.5% halothane at 1–3 Hz and less than 3.5% enflurane at 2–3 Hz; 3.5% enflurane was less depressant than 1.5% halothane at 2 Hz.

Figure 5 plots the anesthetic depression of contractions at 3 Hz, near the approximate physiologic heart rate in the guinea pig. Results are plotted for depression in the presence of diltiazem, and in its absence. At 1 or at 2 MAC, the fractional depression caused by each anesthetic concentration did not differ in the absence or presence of diltiazem. For halothane and isoflurane, the doubling of anesthetic concentration significantly increased the amount of contractile depression.

Discussion

In this study of isolated myocardium, the presence of the calcium entry blocker diltiazem did not significantly alter the depressant actions of the commonly used volatile anesthetics. The combination of diltiazem with either isoflurane, halothane, or enflurane caused myocardial depression which can be described as simply additive, while the previously described differences among the anesthetics remained apparent.

The mechanism of diltiazem negative inotropy is thought to involve primarily blockade of slow-channel Ca^{2+} entry. This blockade decreases the Ca^{2+} available for accumulation and release by the intracellular Ca^{2+} store, the sarcoplasmic reticulum. During sustained rest (≥5 minutes) or low stimulation rates, the guinea pig myocardium soon becomes depleted of Ca^{2+}, as long as there is a normal concentration of external Na (16). Therefore, tension development after rest and at low stimulation rates (≤0.25 Hz) requires Ca^{2+} entry from outside the cell. At higher stimulation rates (≥2 Hz), there is repeated Ca entry with each action potential, so that the sarcoplasmic reticulum will accumulate a large store of Ca^{2+}. This large store of Ca^{2+} in the sarcoplasmic reticulum is released with each depolarization in order to cause tension development (17), and then is reaccumulated to cause relaxation. Diltiazem causes modest blockade of calcium channels when depolarization occurs after rest, but causes increased blockade as the stimulation rate is increased (18,19). The frequency-dependent blockade of calcium channels by diltiazem is similar to the frequency-dependent blockade of sodium channels by local anesthetics. The evidence that the positive force-frequency staircase was maintained in the presence 0.1 μM diltiazem with no selective depression of contractions at 2–3 Hz supports the idea that modest blockade of Ca^{2+} entry by diltiazem is apparently counteracted by a gradual yet substantial accumulation of Ca^{2+} into the sarcoplasmic reticulum with the repeated depolarizations. In contrast, with higher supraclinical diltiazem concentrations (1–10 μM) there is frequency-dependent contractile depression that becomes prominant at and above 1 Hz stimulation rates. These effects at the higher diltiazem concentrations would be anticipated if the frequency-dependent depression of Ca^{2+} entry at 2–3 Hz inhibits so much Ca^{2+} entry that far less can accumulate in the sarcoplasmic reticulum. Thus, there would be insufficient Ca^{2+} accumulated and released by the sarcoplasmic reticulum to develop the normal positive force-frequency response. The frequency-dependent blockade of calcium channels by diltiazem is reflected in frequency-dependent contractile depression, but only when higher drug concentrations are employed. Such variation in frequency-dependent diltiazem depression of contractions as a function of drug concentration probably reflects the complexity of Ca^{2+} handling in myocardium, although additional effects of diltiazem beyond Ca^{2+} entry blockade could also explain these results.

The lower diltiazem concentration employed in this study (0.1 μM or 42 ng/ml), which did not show frequency-dependent contractile depression, was approximately that free drug concentration which would be anticipated clinically. After a 120-mg oral diltiazem dose, peak plasma levels of 100–200 ng/ml have been observed (20), which would correspond to free drug levels of 22–44 ng/ml, assuming 78% protein binding of drug (21). The depression of peak tension and dT/dt-max to approximately 85% of control is similar to depression of isolated tissue (22) and of ventricular performance in animals (23). The 1 μM-diltiazem concentration did show the frequency-dependent contractile depression and was employed to ascertain whether greater calcium channel blockade when combined with subsequent contractile depression by 2 MAC anesthetics would result in enhanced contractile depression.

Contractile depression by 1.7 and 3.5% enflurane

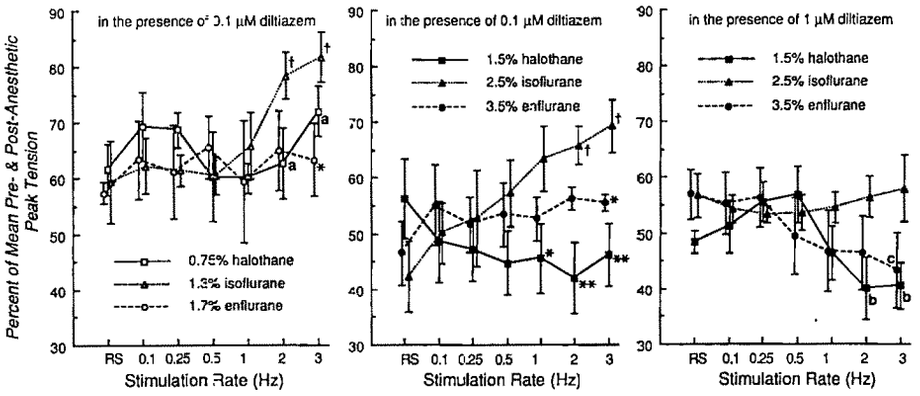


Figure 4. Anesthetic depression of contractility caused by approximately 1 or 2 MAC of anesthetic in the presence of 0.1 or 1.0 μM diltiazem. Anesthetic depression is expressed as a percentage of the average value observed in diltiazem before anesthetic and postanesthetic according to equation 2, and employs the same experiments as shown in Figure 3. This procedure eliminates any variation introduced due to the diltiazem alone. Isoflurane was significantly less depressant at 2–3 Hz, than it was after rest (RS) up to 0.5 Hz (†). $^{**}P < 0.01$; $^{*}P < 0.05$ different from isoflurane by ANOVA, Duncan's multiple range test; a, $P<0.05$ different from isoflurane by paired t-test ($n = 5$, subset of experiments); b, $P < 0.05$ different from isoflurane by paired t-test ($n = 4$, subset of experiments); c, $P < 0.05$ different from isoflurane by paired t-test ($n = 3$, subset of experiments).

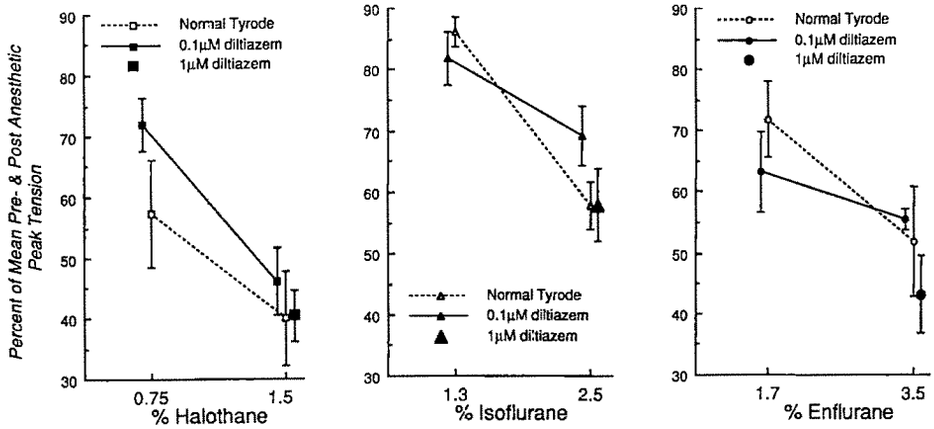


Figure 5. The dose dependence of anesthetic depression of contractility at 3 Hz (physiologic rate for guinea pig). The anesthetic effect at approximately 1 and 2 MAC is shown for normal Tyrode solution (from Ref 5, Fig. 3; and Fig. 2 of this report) and in the presence of 0.1 or 1.0 μM diltiazem. Anesthetic depression is expressed as a percent of the average value observed before anesthetic and during postanesthetic recovery (according to equation 2).

(~1 and 2 MAC) was to 75 and 50% of control, respectively. Although 1.7% enflurane depressed dT/dt-max at 0.5–3 Hz less than at lower stimulation rates, the depressant effects of enflurane were largely independent of stimulation rate. Modest frequency-dependent depressant effects by enflurane have been previously reported: in experiments in cat papillary muscle performed at 27°C and using stimulation rates of 0.003–0.3 Hz; 0.35 mM enflurane (equivalent to ~1%) caused less depression of dT/dt-max and also of peak tension at the higher stimulation rates (24). The depressant actions defined for enflurane can be directly compared with those previously reported for halothane and isoflurane upon contractions accompanying normal action potentials, because these experiments were performed in an identical setting (5). For an equivalent MAC, peak tension was depressed to a similar extent by all three anesthetics after rest and up to 0.5 Hz. However, at stimulation rates of 2–3 Hz, enflurane's effects on contractility as assessed by peak tension and dT/dt-max were generally less depressant than halothane, but more depressant than isoflurane for the same MAC. In the previous study employing contractions accompanying slow action potentials, depressant potency by the anesthetics was halothane ≥ enflurane> isoflurane (5).

The mechanisms by which clinically relevant concentrations of anesthetics depress myocardial contractility include depression of slow-channel–mediated Ca^{2+} entry (3–5) and alteration of Ca^{2+} uptake and release by the sarcoplasmic reticulum (6–10). Furthermore, halothane and isoflurane also show a modest depression of actin-myosin ATPase (25,26). It is noteworthy that at no stimulation rate did diltiazem appear to magnify the depressant effects of the anesthetics. This was true after rest and at low stimulation rates, when external Ca^{2+} entry predominantly activates contractions, and at 2–3 Hz stimulation, when activator Ca^{2+} is derived from the sarcoplasmic reticulum. When the multiple depressant

mechanisms attributable to anesthetics combined with the calcium channel blockade by diltiazem, the resulting contractile depression did not differ from a prediction which assumed simple additive depression, as shown in Figure 3. Halothane causes more Ca^{2+} entry blockade than does isoflurane (5), and is also more potent than isoflurane in decreasing the amount of rapidly released Ca from the sarcoplasmic reticulum, thereby contributing to halothane's greater depression of contractility (6,10). Although halothane was more depressant than isoflurane, when combined with diltiazem, halothane did not cause more nor did isoflurane cause less depression than predicted. In the presence of diltiazem, the anesthetics demonstrated the same pattern of depressant actions as in its absence: at rest and ≤0.25 Hz, equivalent concentrations of isoflurane, halothane, and enflurane caused equivalent depression; at near-physiologic stimulation rates (2–3 Hz), the potency of contractile depression was halothane > enflurane > isoflurane. Thus, isoflurane persisted in showing less depression at 2–3 Hz in the presence of diltiazem, while the lack of frequency-dependent depression remained evident for halothane and enflurane. The additional Ca^{2+} entry blockade produced by 1.0 μM diltiazem, even when sufficient to block the positive force-frequency response, did not alter the depression by an anesthetic even when its mechanisms involve comparatively more Ca^{2+} entry blockade and/or more decrease in internal Ca^{2+} release.

The dose dependence of anesthetic depression did not appear altered by the presence of diltiazem. However, individual muscles were not exposed to multiple concentrations of the same anesthetic so that detailed dose-response curves for each anesthetic were not obtained. Therefore, slopes of the anesthetic dose-responses in the absence and presence of diltiazem could not be directly compared. However, comparison of the depression due to anesthetics (1 or 2 MAC) in the absence and presence of diltiazem (Fig. 5), as well as the comparison of the observed depression with the prediction of combined depression (Fig. 3) suggests that there is no synergistic effect at the concentrations employed. Nevertheless, when higher concentrations of anesthetics and diltiazem are combined, the resultant additive depression may be profound.

Although few detailed mechanistic conclusions may be drawn, Ca^{2+} entry blockade by diltiazem does not appear to potentiate the variety of mechanisms by which the volatile anesthetics interfere with excitation–contraction coupling in myocardium. The simply additive behavior suggests that, at least in certain regards, diltiazem and the anesthetics do not interact at the molecular level. For example, it would seem unlikely that depression of Ca^{2+} entry by halothane involves an alteration in the calcium channel which enhances diltiazem binding. Such a change would cause more calcium channel blockade by diltiazem in the presence of halothane than in its absence, resulting in increased blockade of Ca^{2+} entry by diltiazem. Such additional block of Ca^{2+} entry, when combined with the anesthetics' intrinsic depressant effects, would be expected to cause enhanced, not merely additive, depression of contractility. However, the presence or absence of such interactions requires testing by more sophisticated methods, such as voltage clamping of inward Ca^{2+} currents.

In two previous studies the combination of calcium blocker and volatile agents have been studied. Diltiazem and isoflurane caused additive depression in guinea pig atria (27), while the combination of halothane and verapamil caused additive depression in rabbit papillary muscle, although recovery appeared to be prolonged (28). In these cases, calcium channel blockade did not appear to markedly potentiate contractile depression by the volatile anesthetics.

Administration of calcium channel blockers in conscious animals and patients results in little change in ventricular performance because drug-induced vasodilatory effects result in a baroreceptor-mediated increase in sympathetic tone (22,29). The decrease in blood pressure caused by diltiazem results in increased sympathetic tone which offsets the depression of cardiac contractility caused by depression of calcium entry; this frequency results in improved ventricular performance. Furthermore, this increase in sympathetic tone may not be completely ablated by β-adrenergic blockage (30). Previous work in whole animals has shown that the addition of volatile anesthetics to a diltiazem infusion, or alternately the administration of diltiazem to a previously established volatile agent anesthetic, results in depression of cardiac function as assessed by cardiac output (12,13). In those studies of whole animals, alteration in sympathetic tone within the animals could not be separated from the direct effects of the volatile agents and diltiazem in depressing cardiac function. Depression of the sympathetic response by volatile anesthetics, or possibly the anesthetic state produced by a variety of agents, may permit the appearance of the depressant action of diltiazem. Superimposed on this would be the depression of myocardial contractility directly by the volatile anesthetics. In chronically prepared dogs, there is minimal depression by addition of diltiazem in the presence of a halothane anesthetic, unless there is accompanying blockade of

sympathetic responses by propranolol (14). The present results suggest that additive dose-dependent depression of myocardial function can be expected if the sympathetic responses are blunted or absent, and this depression can be profound at high concentrations.

In contrast to its additive, predictable effects on contractility, diltiazem in combination with the volatile anesthetics have resulted in marked depression of atrioventricular (AV) conduction in animal models (12,13) as well as patients (31). Excitation–contraction coupling involves many steps and is depressed in a graduated manner. At physiologic rates of contraction, release of intracellular Ca^{2+} stores from the sarcoplasmic reticulum is largely responsible for supplying Ca^{2+} to activate contractions. Furthermore, in ventricular (and atrial) myocardium, the normal sodium-dependent action potential provides sufficient depolarization to activate unblocked calcium channels and permit continued Ca^{2+} entry. In contrast, AV conduction involves only slow (calcium channel) action-potential conduction through the AV node. After a certain fraction of calcium channels are blocked or inhibited by diltiazem and by anesthetics, conduction fails. Conduction will cease even though some slow channels remain unblocked, because an insufficient number of active channels remain to sustain a propagated action potential. Although the volatile agents appear to inhibit ion movement through calcium channels, it seems unlikely that these anesthetic molecules "plug" the channel as suggested by diltiazem. While depression of Ca^{2+} entry by diltiazem and anesthetics does not depress Ca^{2+} entry in a manner that synergistically depresses contractility, depression by both drug types together is sufficient to cause failure of AV conduction under certain circumstances.

In summary, the combination of diltiazem and volatile anesthetics results in a predictable, additive depression of myocardial contractility. At physiologic heart rates the order of depressant potency of equianesthetic concentrations is halothane ≥ enflurane > isoflurane, an order observed in the presence of diltiazem, as well as its absence.

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Sixty Years Ago In

Anesthesia & Analgesia

A. E. Guedel and R. M. Waters: A new intratracheal catheter. Current Researches in Anesthesia & Analgesia 1928;7:238–9.

At the time this article was written, Arthur Guedel was head of the Department of Anesthesia at the Indiana University School of Medicine. Ralph Waters was chairman of the new Department of Anesthesia at the University of Wisconsin, which was by today's standards the first and, in 1928, the only academic research department in the world. Each was on his way to becoming a giant in the history of anesthesia in the decades between 1920 and World War II. In this article they join together to describe an innovation destined to revolutionize the practice of anesthesia. Intratracheal catheters had been described before. Indeed, on page 201 of the same issue of this journal, F. W. Green from Melbourne, Australia (this was indeed the journal of a truly *International* Anesthesia Research Society) describes use of a catheter for the intratracheal administration of ether. What Green used was what we mean today by a catheter: a long, thin rubber tube with a distal opening. Green used it to insufflate ether into the trachea, not to occlude the tracheal lumen and provide an airtight fit. What Guedel and Waters describe is a means for the "closed intratracheal administration of any inhalation anesthetic agent by the carbon dioxide method of Ralph M. Waters." Their "catheter" was what we today would call an endotracheal tube: 14 inches long, made of rubber in such a way as to decrease the tendency to kink or collapse, it had an internal diameter of ⅜ inch (!) and a wall thickness of 1/16 inch. It also had a 1½ inch "inflation bag" (i.e., cuff) at the distal end, a "bag" made of rubber with an attached "inflation tube" used to fill the "bag" with air. The result was an airtight system that prevented aspiration of blood, mucous or gastric contents while allowing use of a closed system anesthesia circuit and, ultimately, positive pressure ventilation when, in later years, the need for such became recognized. Cuffed endotracheal tubes were not immediately widely and routinely used, but from this time on, the administration of inhalation anesthesia would never again be what it was before this 1928 paper.

Comparative Motor-Blocking Effects of Bupivacaine and Ropivacaine, A New Amino Amide Local Anesthetic, in the Rat and Dog

Hal S. Feldman, BSc, and Benjamin G. Covino, PhD, MD

FELDMAN HS, COVINO BG. Comparative motor-blocking effects of bupivacaine and ropivacaine, a new amino amide local anesthetic, in the rat and dog. Anesth Analg 1988;67:1047–52.

Ropivacaine (S-(-)-1-propyl-2',6'-pipecoloxylidide) is a new local anesthetic that is structurally related to mepivacaine and bupivacaine. The comparative effects of ropivacaine and bupivacaine on motor function were assessed in the laboratory rat and dog. (It was not possible to accurately evaluate sensory blockade in these models.) Several concentrations of both agents were injected in the region of the sciatic nerve of the rat and into the lumbar epidural or subarachoid space in the dog. Epidural blockade was also performed utilizing solutions of ropivacaine and bupivacaine which contained epinephrine (1:200,000). The rat sciatic block studies indicate that at concentrations of 0.5 and 0.75%, ropivacaine had a slightly shorter time of onset and duration of motor blockade than did bupivacaine. In the epidural and spinal studies in the dog, ropivacaine was less potent and had a shorter duration of motor blockade than did bupivacaine at equal drug concentrations. A 1.0% solution of ropivacaine produced epidural motor blockade similar in onset and duration to that achieved with a 0.75% solution of bupivacaine. Epinephrine did not significantly prolong the duration of motor blockade of either agent after epidural administration.

Key Words: ANESTHETICS, LOCAL—ropivacaine; bupivacaine. ANESTHETIC TECHNIQUES—spinal; epidural.

Ropivacaine (LEA-103; (S-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride monohydrate) is a new amino amide local anesthetic structurally related to mepivacaine and bupivacaine (Fig. 1). Ropivacaine differs from mepivacaine and bupivacaine in that it is an S-isomer, whereas the latter agents are racemic mixtures. In terms of physical chemical properties, the pK_a of ropivacaine is similar to that of bupivacaine (1), but ropivacaine is less lipid soluble than is bupivacaine (2). In isolated rat vagus nerve preparations, ropivacaine is less potent than bupivacaine in blocking Aβ fibers, but is more effective than bupivacaine in the blockade of Aδ and C-fibers (1). In addition, the uptake of ropivacaine by nerve membrane and epidural and subarachnoid fat was less than that of bupivacaine, which is consistent with its lower partition coefficient (2). Little detailed information is available concerning the comparative anesthetic properties of ropivacaine and bupivacaine in intact animals. Preliminary results indicate that ropivacaine is similar to bupivacaine in terms of sciatic nerve blockade and epidural anesthesia in the guinea pig (3).

The current study was initiated to evaluate the relative efficacy of ropivacaine and bupivacaine as local anesthetic agents for sciatic nerve blockade in the rat and for epidural and spinal anesthesia in the dog.

Methods

Experiments reported herein were reviewed and approved by the committee on laboratory animal care and use. Animals were maintained in accordance with all federal and state laws regarding the care and use of laboratory animals and the guidelines established by the American Association of Laboratory Animal Care.

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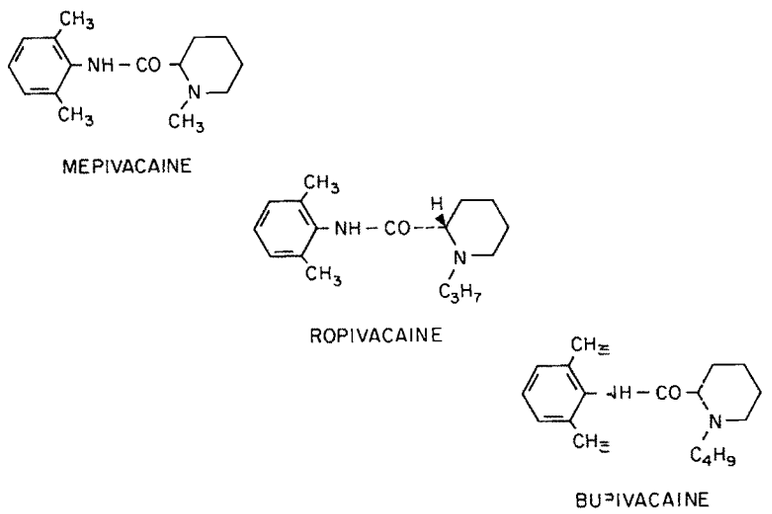

Figure 1. Chemical structures of mepivacaine, ropivacaine, and bupivacaine.

Sciatic Nerve Blockade in the Rat

Sciatic nerve blockade was performed by the method formerly described (4) in male Sprague-Dawley rats with a mean (± SEM) weight of 359.5 ± 2.1 grams (range 250–500). Initially, solutions containing 0.25% ropivacaine (n = 40) or 0.25% bupivacaine (n = 40) were injected. (Solutions utilized in the studies reported herein were supplied by Astra Alab, AB, Sweden, and Astra Pharmaceutical Products, Inc., USA.) Animals were injected in a random unblinded fashion. After these initial studies, a blinded crossover study was conducted in 40 rats. The solutions employed were 0.5 and 0.75% bupivacaine, 0.5, 0.75, and 1.0% ropivacaine, and 0.9% saline as a control. Each animal was injected in both hind limbs with each solution; (n = 80 for each of the various solutions). The order of administration was randomized and 48 hours elapsed between injections into the same hind limb. The volume of injectate was kept constant at 0.1 ml. Onset of motor blockade was defined as the time from injection to the time when the animal lost motor control of the foot as evidenced by dragging the hind limb and/or by closing of the foot with digits together, as compared to a normal foot with digits open and far apart. Duration of motor blockade was defined as the time from onset of motor blockade to the time when these signs disappeared. At the termination of the study, rats were killed by carbon dioxide inhalation. Five rats from each group were selected at random and injection sites were dissected and examined for evidence of visible lesions.

Statistical analysis consisted of analysis of variance and Tukey test, and statistical significance was considered achieved at the $P < 0.05$ level. Only data from rats that demonstrated motor blockade were utilized for statistical analysis and calculation of mean (± SEM) values.

Epidural and Subarachnoid Administration in the Dog

Surgical preparation for the epidural and subarachnoid injections was similar to that previously described (5). At least 48 hours before the start of the experiment, dogs were anesthetized with 20 mg/kg IV thiamylal. The lumbar region of the back was shaved and cleansed for surgery. The animal was placed on the surgical table in the prone position. The hind limbs were extended cranially to maximally separate the lumbar vertebrae. The table was placed in the head-up position. An 18-gauge, thin-wall Crawford epidural needle was then inserted percutaneously into the subarachnoid or the epidural space. The catheter was then directed through the needle until the tip of the catheter lay 1–2 cm beyond the tip of the needle. The needle was removed and the outside length of the catheter trimmed. The trimmed catheter was then attached to a Schraeder-type valve made of Teflon. The valve was sutured subcutaneously with the hub exposed. Both epidural and subarachnoid injections were made through this valve and catheter. The epidural space was identified by the loss of resistance technique and the subarachnoid implantations were positively identified by the free flow of cerebrospinal fluid through the hub of the needle and/or the catheter. Onset of motor blockade for both types of injection was defined as the time between completion of the injection and the time when the dog's hind limbs were unable to support its weight. The duration of motor blockade was defined as the time from onset of motor blockade to the time

when the animal was able to support its own weight. Sensory blockade was not evaluated in the present study.

Volume of injectate was kept constant at 1.0 ml for the subarachnoid injections and 3.0 ml for the epidural injections. In both cases the injections of local anesthetic were followed by 0.5 ml flush of vehicle. Concentrations in the subarachnoid studies were ropivacaine 1.0 and 0.75%, and bupivacaine 0.75 and 0.5%. In the epidural studies, concentrations of 0.25, 0.5, 0.75, and 1.0% ropivacaine, and 0.25, 0.5, and 0.75% bupivacaine were employed.

Eight male mongrel dogs having a mean weight of 19.1 ± 0.9 (± SEM) kg were utilized in the spinal studies. The dogs were randomly treated with the four anesthetic solutions. A period of at least 24 hours was allowed to elapse between individual drug injections. The initial epidural study employed 52 mongrel dogs (24 males, 28 females) having a mean weight of 19.7 ± 0.45 kg. These animals were randomly given ropivacaine (0.25, 0.5, 0.75, and 1.0%) and/or bupivacaine (0.25, 0.5, and 0.75%). At least 24 hours elapsed between individual drug injections. The number of animals given each concentration of ropivacaine is as follows: 0.25%, 11; 0.5%, 30; 0.75%, 26; 1.00%, 29. The number of animals given each concentration of bupivacaine is as follows: 0.25%, 17; 0.5%, 23; and 0.75%, 60.

In a separate group of 12 mongrel dogs (6 male, 6 female), epidural injections were performed using solutions of bupivacaine or ropivacaine with and without epinephrine (1:200,000). The dogs having a mean weight of 18.7 ± 1.42 kg (SEM) were randomly assigned to two drug treatment groups. There were six dogs in each treatment group. However, one dog in the bupivacaine group was excluded from the study for technical reasons. Each dog within a treatment group received either bupivacaine 0.75, 0.5, and 0.25% with and without epinephrine, or ropivacaine 0.25, 0.5, 0.75, and 1.0% with and without epinephrine. The solutions were administered in a random, unblinded fashion, and a minimum recovery time of 24 hours was allowed between injections.

Statistical analysis of the data was performed in the same fashion as described for the rat sciatic block studies. $P < 0.05$ was considered statistically significant.

Results

Rat Sciatic Nerve Block

The results of the studies in rats are summarized in Table 1. In the initial studies in which 0.25% solutions were injected, no difference between the two agents was observed with regard to the frequency of block or time of onset of motor block. In the blinded portion of the study, in which several concentrations of both agents were employed, no difference in the frequency of block was observed between drugs and between the various concentrations. However, 0.5 and 0.75% solutions of ropivacaine had a statistically significant shorter time to onset of motor blockade than did the same concentration of bupivacaine ($P < 0.05$). For some unexplained reason, the 1.0% ropivacaine solution resulted in a longer onset time than did the 0.75% solutions. Motor blockade was not observed in any of the animals receiving blinded injections of saline solution.

Table 1. Times of Onset and Duration of Rat Sciatic Motor Blockade with Ropivacaine and Bupivacaine (min)

Drug	N	B	Onset of ($\bar{X}$ ± SEM)		Duration of ($\bar{X}$ ± SEM)	
Ropivacaine 1.00%	80	80	4.4 ± 0.2		155.9 ± 2.2	
Ropivacaine 0.75%	80	76	3.0 ± 0.1	*	143.3 ± 1.9	*
Bupivacaine 0.75%	80	79	5.1 ± 0.2		158.0 ± 3.7	
Ropivacaine 0.50%	80	77	5.0 ± 0.2	*	147.1 ± 2.1	
Bupivacaine 0.50%	80	72	7.9 ± 0.3		160.6 ± 3.9*	
Ropivacaine 0.25%	40	36	7.4 ± 0.4	NS	100.0 ± 3.1	NS
Bupivacaine 0.25%	40	32	6.8 ± 0.4		102.4 ± 3.9	
Saline 0.90%	80	0	—		—	

*Significant at $P < 0.05$.
NS, not significant.
Abbreviations: N, number of nerves injected; B, number of limbs with motor block.

Ropivacaine- (0.5 and 0.75%) produced motor block was significantly shorter in duration than that produced by the same concentrations of bupivacaine ($P < 0.05$). However, the duration of action of 1.0% ropivacaine was not significantly different than that of 0.5 and 0.75% bupivacaine.

There were no signs of adverse reactions, irreversible blocks, or other sequelae in any of the animals. In addition, there were no grossly visible lesions observed at the site of injection in any animal examined post mortem.

Subarachnoid Injection

Onset of motor blockade ranged from 1.7 ± 0.4 minutes in the 1.0% ropivacaine group to 4.1 ± 1.1 minutes in the 0.5% bupivacaine group (Table 2). There was no statistically significant difference in onset time between the various anesthetic solutions. Duration of motor blockade ranged from 103.3 ± 18.7 minutes for 0.75% ropivacaine to 163.4 ± 13.0 min-

Table 2. Times of Onset and Duration of Motor Blockade after Subarachnoid Administration of Ropivacaine and Bupivacaine

Drug	N	Onset*	Duration*
Ropivacaine 1.00%	5	1.7 ± 0.4	127.5 ± 8.3
Ropivacaine 0.75%	4†	2.8 ± 0.5	103.3 ± 8.7
Bupivacaine 0.75%	5	2.6 ± 0.7	163.4 ± 8.0
Bupivacaine 0.50%	5	4.1 ± 1.1	156.3 ± 0.5

*Values are mean ± SEM (min).
†One dog was eliminated from analysis because of technical failure.

utes for the 0.75% bupivacaine (Table 2). Although the mean duration of motor blocks was shorter in dogs given ropivacaine, no statistically significant difference existed in duration of motor blockade between any of the groups, probably due to the small number of animals in each group. There were no adverse reactions associated with the subarachnoid administration of either drug.

Epidural Injection

Solutions of 0.25% ropivacaine and bupivacaine failed to produce complete loss of weight support in any of the animals (Table 3). Although overall frequency of blockade with 0.5% bupivacaine was greater (70%) than that seen with 0.5% ropivacaine (47%), the difference was not statistically significant as determined by χ^2 analysis. Onset of motor blockade varied between 5 and 9 minutes in both drug groups. In both drug groups onset of motor blockade was inversely related to dose. The lowest effective concentrations of both drugs had significantly longer onset times than did the most concentrated solution ($P < 0.05$). No statistically significant difference in onset times existed between the same concentrations of both agents.

The duration of motor blockade was prolonged as the concentration of both agents increased. Duration of motor blockade ranged from 141.4 ± 12.7 minutes for 0.5% ropivacaine to 258.6 ± 10.9 minutes with 0.75% bupivacaine. Statistical comparison within a drug group showed a significant difference between low and high concentrations. No statistically significant difference existed between the 0.5% concentrations of ropivacaine and bupivacaine. However, 0.75% bupivacaine had a significantly longer duration of motor block than the same concentration of ropivacaine. No statistically significant difference in duration existed between 1.0% ropivacaine and 0.75% bupivacaine or between 0.75% ropivacaine and 0.5% bupivacaine.

The results of the second epidural study in which solutions of plain and epinephrine-containing solutions were employed are summarized in Table 4. Both 0.25% bupivacaine and 0.25% ropivacaine with and without epinephrine failed to produce complete motor blockade in any of the animals. Frequency of block with 0.5% plain ropivacaine was 17%, compared with 80% in the 0.5% plain bupivacaine group. Epinephrine (1:200,000) increased the frequency of motor blockade from 17 to 83% with 0.5% ropivacaine, and from 80 to 100% with 0.5% bupivacaine. The increase with ropivacaine was statistically significant. Complete motor block occurred in all the dogs in which higher concentrations of ropivacaine and bupivacaine with and without epinephrine were employed.

Mean onset time of motor blockade ranged from 4.5 ± 0.7 minutes for the 0.75% plain bupivacaine solutions to 10.9 ± 2.5 minutes for the 0.5% ropivacaine with epinephrine solution. No statistically significant difference in onset time existed between any of the various solutions.

Duration of motor blockade in both the ropivacaine and bupivacaine groups tended to increase as the concentration of the anesthetic solution was increased. The addition of epinephrine to 0.5% and 0.75% solutions of bupivacaine and 0.75% and 1.0% solutions of ropivacaine did not significantly increase the duration of motor blockade. At equal concentrations, solutions of bupivacaine with and without epinephrine produced a significantly longer duration of motor block than did ropivacaine solutions with and without epinephrine. There was no statistically significant difference between 1.0% ropivacaine with epinephrine and 0.75% bupivacaine without epinephrine. However, 0.75% bupivacaine with epinephrine produced a significantly longer duration of motor block than 1.0% ropivacaine with epinephrine. No systemic adverse effects were observed in any of the animals.

Discussion

Sciatic nerve block in the rat provides a means of assessing, in relatively large numbers of animals, the onset and duration of motor blockade produced by local anesthetics. Sciatic nerve block also provides information regarding potential neurotoxicity of local anesthetic drugs. Results of the current study indicate that ropivacaine, a new amino amide agent, is similar in terms of potency of motor blockade to bupivacaine, though onset and duration of motor block produced by ropivacaine are shorter than that of bupivacaine when employed in equal concentrations. Moreover, the agent was free of any gross signs of neural toxicity in the concentrations studied. De-

Table 3. Times of Onset and Duration of Motor Blockade after Epidural Administration of Ropivacaine and Bupivacaine Without Epinephrine

Drug	N	Onset ($\bar{X}$ ± SEM)		Duration ($\bar{X}$ ± SEM)		Frequency of block (%)	
Ropivacaine 1.00%	29/29	5.4 ± 0.3		234.8 ± 14.4		100	
Ropivacaine 0.75%	26/25	7.0 ± 0.5	NS	184.5 ± 10.1	*	96	NS
Bupivacaine 0.75%	61/57	5.7 ± 0.3		258.6 ± 10.9		93	
Ropivacaine 0.50%	30/14	9.3 ± 1.4	NS	141.4 ± 12.7	NS	47	NS
Bupivacaine 0.50%	23/16	7.3 ± 0.6		158.1 ± 30.6		70	
Ropivacaine 0.25%	11/0	NB		NB		0	
Bupivacaine 0.25%	17/0	NB		NB		0	

*Significant at $P \leq 0.05$.
NS, not significant.
Abbreviations: N, number of animals injected/number of successful blocks. NB, no complete motor blockade.

Table 4. Time of Onset and Duration of Motor Block after Epidural Administration of Ropivacaine and Bupivacaine with and without Epinephrine

Drug	N	Onset*	Duration*	Frequency of block (%)
Plain solutions				
Ropivacaine 1.00%	6/6	5.5 ± 1.0	186.3 ± 14.3	100
Ropivacaine 0.75%	6/6	7.5 ± 1.2	144.7 ± 16.9	100
Bupivacaine 0.75%	5/5	4.5 ± 0.7	287.5 ± 31.7†	100
Ropivacaine 0.50%	6/1	9.5	45.5	17
Bupivacaine 0.50%	5/4	8.3 ± 2.6	123.5 ± 13.7	80†
Ropivacaine 0.25%	6/0	NB	NB	0
Bupivacaine 0.25%	5/0	NB	NB	0
With epinephrine 1:200,000				
Ropivacaine 1.00%	6/6	6.0 ± 1.0	209.0 ± 13.3	100
Ropivacaine 0.75%	6/6	6.2 ± 0.6	173.0 ± 26.0	100
Bupivacaine 0.75%	5/5	5.1 ± 0.7	307.2 ± 18.5†	100
Ropivacaine 0.50%	6/5	10.9 ± 2.5	130.3 ± 9.6	83
Bupivacaine 0.50%	4/4	6.4 ± 1.9	156.8 ± 34.2†	100
Ropivacaine 0.25%	6/0	NB	NB	0
Bupivacaine 0.25%	5/0	NB	NB	0

*Values are mean ± SEM (min).
†Significant at $P < 0.05$.
N, number of animals injected/number of successful blocks. NB, no complete motor blockade.

tailed histologic studies in guinea pigs and dogs also indicate that ropivacaine does not cause any localized irritation in peripheral nerves or spinal cord (Astra Alab, AB, Clinical Investigators Manual - LEA-103 [ropivacaine]).

Though our data shows ropivacaine and bupivacaine to be approximately equally potent in producing motor blockade, the data in dogs suggest that ropivacaine is less potent than bupivacaine in blocking motor fibers when injected epidurally because the frequency of motor block achieved with 0.5% ropivacaine was less than that produced by 0.5% bupivacaine. This difference between the rat and dog studies may be related to species differences or may be indicative of a difference between sensitivity of peripheral and central motor fibers to pharmacologic blockade. Studies of the isolate rat vagus nerve also indicate that ropivacaine is less potent than bupivacaine in terms of the concentration required to block large myelinated A-fibers (1). However, ropivacaine appears to be more potent than bupivacaine in terms of conduction block of unmyelinated C-fibers. The difference in motor blocking potency is consistent with the lower lipid solubility of ropivacaine (2).

Differences in rapidity of onset of motor block between ropivacaine and bupivacaine was observed in rats and dogs. At equal concentrations, ropivacaine had a significantly shorter onset time in the rat sciatic block model, but with epidural and intrathecal injections in dogs, no difference in onset times was seen. Onset of conduction block is primarily related to the pK_a values of local anesthetics because it is the base form that diffuses most readily across the nerve sheath and membrane. Because the pK_a of ropiva-

caine (8.0) and bupivacaine (8.1) are similar (1), one would not anticipate a marked difference in onset times between the two agents.

The intact animal studies reported in the present study indicate that the duration of motor block produced by ropivacaine is shorter than that of bupivacaine when equal concentrations of both drugs were employed. Duration may be related to lipid solubility, protein binding, and vasodilator activity of specific agents. Little difference in the plasma protein binding of the two agents exists (K-G Jostell, S. Elofsson, Department of Drug Metabolism, Astra Lakemedel AB, Sweden). Bupivacaine is more lipid soluble than ropivacaine and is taken up by the nerve membrane and epidural fat to a greater extent than ropivacaine (2). The greater uptake in the nerve membrane may be responsible for the longer duration of action of bupivacaine. In addition, the greater uptake by epidural fat may also result in a more prolonged duration because the epidural fat may serve as a depot site for slow release of drug, leading to a prolonged duration. No information is available concerning the peripheral vascular effects of ropivacaine. The failure of epinephrine to significantly prolong the duration of epidural block with either agent suggests that little difference in vascular activity may exist between the two agents when injected into the epidural space. Epinephrine did improve the frequency of motor blockade of both agents when the 0.5% concentrations were administered into the epidural space. These results confirm previous reports in humans that epinephrine increases the depth but not the duration of motor block produced by epidurally administered 0.75% bupivacaine (6).

Differences were noted in the duration of motor blockade after administration of ropivacaine and bupivacaine in the two epidural studies. The reason for these discrepancies is not clear. The number of animals employed in the first epidural study was greater than the number of animals in the second study. These studies were also performed at different times of the year. Chemical analysis of the solutions used in the two studies failed to reveal any significant differences in drug concentration. Although the absolute duration values differed, ropivacaine produced a shorter duration of motor block than that caused by bupivacaine in both epidural studies.

The results of our studies in dogs suggest that ropivacaine may be less potent and produce a shorter duration of anesthesia than bupivacaine. However, in general, the local anesthetic profile of ropivacaine appears to be similar to that of bupivacaine in terms of motor blockade. When employed clinically, durations of anesthesia with 1.0 and 0.75% ropivacaine may equal that of 0.75% and 0.5% bupivacaine, respectively.

Several questions remain unanswered concerning the possible usefulness of this new agent, ropivacaine. The ability of bupivacaine to discriminate between blockade of sensory and motor fibers makes this agent particularly valuable for obstetric analgesia. It is not known whether in vivo ropivacaine produces a similar differential blockade of sensory and motor fibers. Perhaps more important is the possibility of differences in cardiotoxicity of ropivacaine and bupivacaine. Preliminary studies suggest that ropivacaine is less cardiotoxic than is bupivacaine (7–9). However, the therapeutic indexes of ropivacaine and bupivacaine have not been established. Clearly, additional animal and clinical studies are required to evaluate the relative anesthetic value of ropivacaine as compared to bupivacaine.

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Comparative Pharmacokinetics of Bupivacaine and Ropivacaine, a New Amide Local Anesthetic

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ARTHUR GR, FELDMAN HS, COVINO BJ. Comparative pharmacokinetics of bupivacaine and ropivacaine, a new amide local anesthetic. Anesth Analg 1988;67:1053–8.

The pharmacokinetics of ropivacaine, a new amide local anesthetic, and bupivacaine were determined in dogs after IV and epidural administration. After 15-minute IV infusions of 3.0 mg/kg ropivacaine (n = 6) and 3.4 mg/kg bupivacaine (n = 4), the maximum arterial concentrations (C_{max}) of ropivacaine averaged 2.41 ± 0.52 μg/ml compared with 3.35 ± 0.16 μg/ml of bupivacaine. The elimination half life ($t_{1/2\beta}$) of ropivacaine (25.9 ± 1.7 min) was significantly shorter than for bupivacaine (39.1 ± 13.3 min) after IV infusion. This was reflected by mean clearance values (Cl) for ropivacaine of 41.1 ± 8.2 $ml \cdot min^{-1} \cdot kg^{-1}$ compared with 32.3 ± 4.8 $ml \cdot min^{-1} \cdot kg^{-1}$ for bupivacaine, although the difference was not statistically significant. After epidural injections (ropivacaine n = 6; bupivacaine n = 5), a dose-related increase in C_{max} was observed with both drugs. Although C_{max} tended to be higher for ropivacaine, a significant difference was only attained when comparing C_{max} after administration of 0.25% plain solutions of both agents. The addition of epinephrine did not consistently decrease the C_{max} of either agent. The apparent $t_{1/2\beta}$ of both agents was significantly longer after epidural administration than after IV infusion. No differences existed between $t_{1/2\beta}$ values for ropivacaine and bupivacaine after epidural administration. Total body clearance of both agents tended to be lower after epidural administration, particularly when epinephrine-containing solutions were employed. Little difference existed between the two drugs when equivalent solutions were administered. The results of this pharmacokinetic study indicate that after IV infusion of bupivacaine and ropivacaine, concentrations of ropivacaine decrease more rapidly than bupivacaine during the elimination phase. This may result in a greater margin of safety for the new agent. However, after epidural administration, the pharmacokinetic profiles of the two drugs were quite similar.

Key Words: ANESTHETICS, LOCAL—ropivacaine, bupivacaine. PHARMACOKINETICS—ropivacaine, bupivacaine. ANESTHETIC TECHNIQUES, EPIDURAL—ropivacaine and bupivacaine.

Ropivacaine is an amide-type local anesthetic agent that is structurally related to bupivacaine and mepivacaine but, unlike these two agents, ropivacaine is prepared as an isomer: S-(-)-1-Propyl-2′,6′-pipecoloxylidide hydrochloride monohydrate. Initial studies found the n-heptane/buffer partition coefficient for ropivacaine to be intermediate between that of lidocaine and that of bupivacaine, as was its uptake into isolated nerve tissue and extradural fat (1). When applied directly to an isolated rat vagus nerve preparation, ropivacaine was less potent than bupivacaine in terms of conduction block of Aβ fibers, but ropivacaine blocked Aδ and C fibers to a greater extent than did bupivacaine (2). In intact animal models ropivacaine is a local anesthetic agent the potency and duration of action of which may be less than that of bupivacaine (3,4). In dogs, ropivacaine and bupivacaine produce convulsions with similar doses, but ropivacaine may be less cardiotoxic than bupivacaine (5). The current study was designed to determine the pharmacokinetics of ropivacaine and bupivacaine in dogs after both IV and epidural administration and to evaluate the effect of epinephrine on blood concentrations of both agents after epidural injection.

Methods

Studies were approved by the institutional committees on animal care and use. Animals were main-

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tained in accordance with the guidelines of the Committee on Animals of the Harvard Medical School and those prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW (now DHHS) publication no. (NIH) 78-23, revised 1978) or in accordance with guidelines for animal care prepared by the American Association for Accreditation of Laboratory Animal Care.

Intravenous Infusion

Two groups of adult male mongrel dogs weighing 18.5 ± 1.9 kg (mean ± SD, n = 6, ropivacaine) and 17.7 ± 1.5 kg (n = 4, bupivacaine) were used in this part of the study. A polyethylene catheter for blood sampling and blood pressure monitoring was implanted in the abdominal aorta via a femoral artery under IV thiamylal anesthesia (20 mg/kg) and animals were allowed to recover for at least 48 hours before drug infusion. On the experimental day, animals were weighed and then secured in the standing position in a canvas sling. The arterial catheter was flushed with heparinized saline (2,000 units/liter) before being connected to a pressure transducer with arterial blood pressure then being recorded on a Grass polygraph. A lead II ECG was also monitored. A Teflon IV catheter (20-gauge) was inserted percutaneously in a forelimb vein and flushed with heparinized saline. Blood pressure and heart rate were allowed to stabilize prior to start of drug infusion.

The stock drug solutions (1% ropivacaine prepared as drug hydrochloride; Astra Alab AB, Sweden; 0.5% Sensorcaine^R, Astra Pharmaceutical Products, Inc., USA) were diluted with 0.9% saline such that a total dose of 3.4 mg/kg bupivacaine HCl or 3.0 mg/kg ropivacaine HCl would be delivered over 15-min at a rate of 1.7 ml/min. The doses were chosen on the basis of the relative convulsive potency of these agents as previously determined in separate groups of animals using incremental IV bolus injections. Drug was infused into the forelimb vein from a calibrated glass syringe using a syringe infusion pump. Arterial blood samples (3 ml) for measurements of drug concentrations were taken prior to starting the infusion, at 5, 10 and 15 minutes during the infusion and at 1, 3, 5, 10, 15, 20, 30, 60, 90, 120, 150, 180, 230 and 240 minutes after termination of the infusion. Blood samples were stored in 5 ml glass tubes containing sodium heparin and kept at −20°C until analysis. Blood loss was replaced with heparinized saline, which also served to maintain the patency of the catheter throughout the study period. Additional arterial samples for determination of pH, po_2 and pco_2 were taken prior to starting the infusion, at the end of the infusion and at 30 and 60 minutes after terminating the infusion. Heart rate and blood pressure were continuously monitored up to 60 minutes after ending the infusion, at which point animals were removed from the sling.

Epidural Injections

Adult male mongrel dogs were used. Under IV thiamylal anesthesia and aseptic conditions, an 18 gauge catheter was placed percutaneously in the lumbar epidural space utilizing the loss of resistance technique. The preparation for repeated epidural injections was similar to that described previously for spinal anesthesia in the dog (6). A polyethylene catheter was also placed in a carotid artery for blood sampling. A minimum recovery period of 24 hours elapsed prior to experimentation.

The volume of epidural injections was kept constant at 3.0 ml, followed by a 0.5 ml saline flush. One group of six animals (weight 15.5 ± 3.7 kg) had epidural injections of 0.25, 0.5, 0.75 and 1.0% ropivacaine solutions with and without 1:200,000 epinephrine. A second group of five animals (weight 20.8 ± 3.1 kg) had epidural injections of 0.25, 0.5 and 0.75% bupivacaine solutions with and without 1:200,000 epinephrine. Eight epidural injections were performed on each animal in the ropivacaine group and six in the bupivacaine group. All animals were allowed a minimum recovery period of at least 24 hours between injections.

Three-ml blood samples were taken prior to injection of drug, and 5, 10, 15, 20, 25, 30, 40, 60 and 90 minutes after injection. With 0.75 and 1.0% drug solution injections, further samples were withdrawn 120, 150, 180, 210, 240 and 300 minutes after injection. The blood samples were stored as described for the IV infusion.

Drug Concentration and Pharmacokinetic Analysis

Quantitative analysis of ropivacaine and bupivacaine in whole blood was performed by a gas chromatographic technique similar to that described by Tucker (7). The minimum measurable concentration for both drugs was 0.01 μg/ml and the day to day coefficients of variation at 0.10 μg/ml were ±3% for bupivacaine and ±7% for ropivacine. All concentration data in this study are expressed as μg drug hydrochloride per ml whole blood.

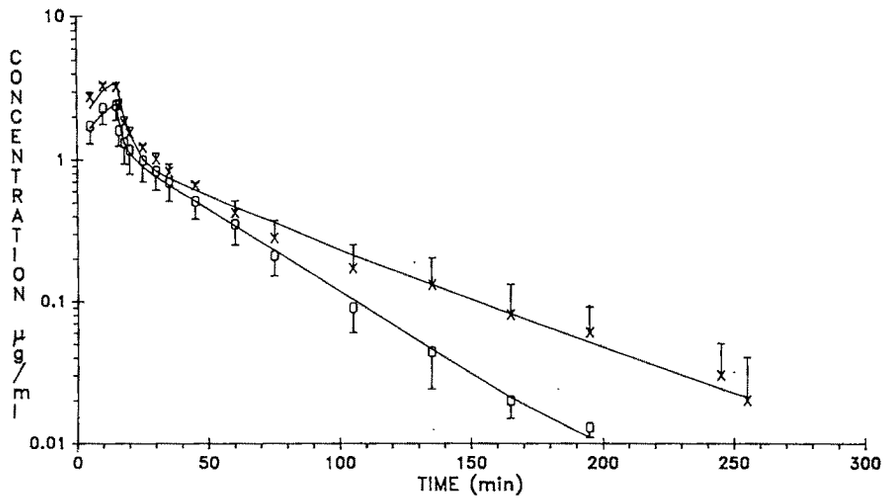

Figure 1. Arterial whole blood concentrations after IV infusions of ropivacaine (3.0 mg/kg, $n = 6$) and bupivacaine (3.4 mg/kg, $n = 4$). Values are means ± SD.

Table 1. Pharmacokinetic Data After IV Infusion of 3.0 mg/kg Ropivacaine ($n = 6$) and 3.4 mg/kg Bupivacaine ($n = 4$)

	C_{max} (μg/ml)	Weight (kg)	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (min)	MBRT (min)	V_c(L/kg)	$V_D$ss (L/kg)
Ropivacaine	2.41 ±0.52	18.5 ±1.9	1.4 ±0.8	25.9† ±1.7	27 ±4	0.26 ±0.13	1.10 ±0.25
Bupivacaine	3.35 ±0.16	17.7 ±1.5	2.1 ±0.3	39.1 ±13.3	37 ±13	0.26 ±0.03	1.17 ±0.31
	Cl (ml·min^{-1}·kg^{-1})	k_{12} (min^{-1})	k_{21} (min^{-1})	k_{10} (min^{-1})	AUC_C (μg/ml·min)	AUC_M (μg/ml·min)	AUMC (μg/ml·min^2)
Ropivacaine	41.1 ±8.2	0.337† ±0.132	0.087† ±0.025	0.189 ±0.081	71.8 ±15.4	72.3 ±15.4	1972 ±519
Bupivacaine	32.3 ±4.8	0.174 ±0.023	0.051 ±0.018	0.127 ±0.030	107.0 ±14.1	106.7 ±13.2	4117 ±1819

†$P < 0.05$, ropivacaine compared to bupivacaine. AUC, AUMC and C_{max} were not compared. C_{max}, peak concentration; $t_{1/2\alpha}$ and $t_{1/2\beta}$, half-lives of distribution and elimination, respectively; MBRT, mean body residence time; V_c, volume of distribution of the central compartment; $V_D$ss, volume of distribution at steady state; Cl, total body clearance; k_{12}, k_{21}, k_{10}, rate constants; AUC_C, area under the drug concentration curve calculated from compartmental analysis; AUC_M, area under the drug concentration curve determined by the trapezoidal rule with extrapolation to infinite time; AUMC, area under the moment curve.

Blood drug concentration data after IV infusion were best described by a two compartment model. The computer program SIMPLEX (provided by Dr. J.A. Clements, Department of Pharmacy, Heriot-Watt University, Edinburgh, Scotland) was used for these analyses, utilizing an 'opportunistic' non linear regression method based on the algorithm of Nelder and Mead (8). Data points were weighted according to the method of Ottaway (9) which, in this instance, applies greater weighting to the lower concentrations during the elimination phase of drug. Compartmental modeling of concentration data after epidural injection of drug was inadequate due to the limited number of data points during the absorption phase. Thus, pharmacokinetic information from this part of the study is limited to data obtained by noncompartmental analysis according to the techniques outlined by Tucker (10). Only the concentration data from 0.75 and 1.0% epidural drug injections were subjected to pharmacokinetic analysis.

Statistical analysis of data was accomplished utilizing analysis of variance followed by the Tukey test, and Student's *t*-tests for paired or unpaired data where appropriate. A P value of <0.05 was considered statistically significant. Data are expressed as means ± SD.

Results

Intravenous Infusion

After IV infusion of 3.0 mg/kg ropivacaine, transient head tremors were observed in one of six animals. Heart rate, blood pressure, and blood gas values were not significantly altered during the experimental period. Peak arterial ropivacaine concentrations

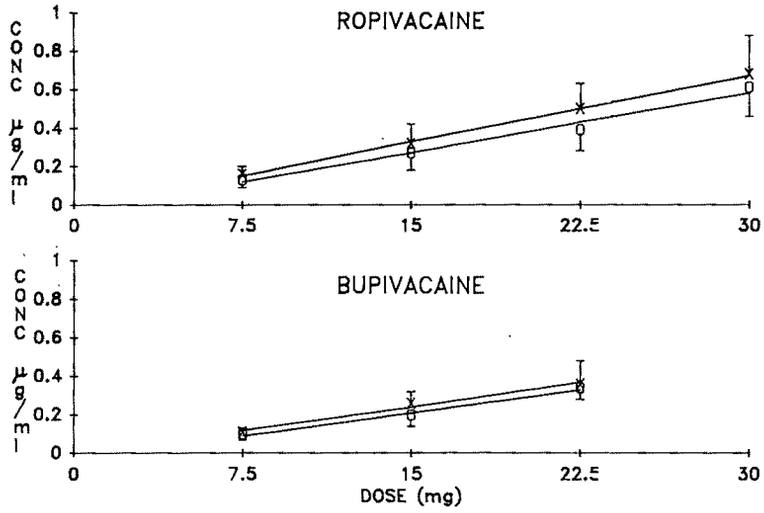

Figure 2. Mean peak arterial concentrations of ropivacaine and bupivacaine after epidural injection. $P < 0.05$—bupivacaine 7.5 mg (0.25%) plain compared with ropivacaine 7.5 mg (0.25%) plain, and $P < 0.05$ ropivacaine 15 mg (0.5%) plain compared with ropivacaine 15 mg (0.5%) with epinephrine.

Table 2. Pharmacokinetic Data After Epidural Administration of Ropivacaine and Bupivacaine†

	Bupivacaine		Ropivacaine			
	0.75% plain	0.75% epinephrine	0.75% plain	0.75% epinephrine	1.0% plain	1.0% epinephrine
Dose (mg)	22.5 —	22.5 —	22.5 —	22.5 —	30.0 —	30.0 —
Weight (kg)	20.8 ± 3.1	20.8 ± 3.1	15.5 ± 3.7	15.5 ± 3.7	15.5 ± 3.7	15.5 ± 3.7
$t_{1/2\beta}$ (min)	168 ± 33*	218 ± 47*	201 ± 89*	202 ± 37*	190 ± 106*	196 ± 74*
Cl ($ml \cdot min^{-1} \cdot kg^{-1}$)	35.3 ± 6.2	24.6 ± 4.0*	25.3 ± 7.6*	24.6 ± 5.2*	30.3 ± 12.0	26.8 ± 9.4*
MBRT (min)	226 ± 50*	297 ± 66*	268 ± 105*	267 ± 47*	260 ± 158*	262 ± 101*
C_{max} (μg/ml)	0.36 ± 0.12	0.34 ± 0.06	0.50 ± 0.13	0.39 ± 0.11	0.68 ± 0.20	0.61 ± 0.15

*$P < 0.05$ compared with IV data.
†Values are means ± SD.

(C_{max}) averaged 2.41 ± 0.52 μg/ml, with a range of 1.56 to 3.07 μg/ml. When the drug infusion was terminated, concentrations decreased rapidly in a biphasic manner (Fig. 1). The IV dose of bupivacaine of 3.4 mg/kg resulted in transient head tremors in three of four animals. There were no significant changes in heart rate, blood pressure, or blood gas tensions during the study. The mean C_{max} of bupivacaine was 3.35 ± 0.16 μg/ml (range 3.31–3.51 μg/ml), which was greater than that for ropivacaine. All volume of distribution terms for both drugs were similar but $t_{1/2\beta}$ for ropivacaine (25.9 ± 1.7 min) was significantly less than for bupivacaine (39.1 ± 3.3 min) (Table 1). Mean total body clearance of ropivacaine (41.1 ± 8.2 $ml \cdot min^{-1} \cdot kg^{-1}$) was greater than for bupivacaine (32.3 ± 4.8 $ml \cdot min^{-1} \cdot kg^{-1}$), although the difference was not statistically significant. No differences were seen in the k_{10} rate constants, but k_{12} and k_{21} were significantly greater for ropivacaine.

Epidural Injection

Peak arterial concentrations of both drugs, either with or without epinephrine, occurred in blood samples taken 5 or 10 minutes after injection into the epidural space. No arterial concentrations >1.0 μg/ml were observed. Mean peak arterial drug concentrations, regardless of time of occurrence, are presented in Figure 2 and Table 2. All mean peak blood concentrations of bupivacaine were slightly lower than for ropivacaine at equal doses of drug, but statistical significance was only attained when comparing the 0.25% plain solutions. Epidural injection of epinephrine containing solutions resulted in mean peak arterial concentrations lower than those after injection of solutions without epinephrine. However, statistical significance occurred only when comparing mean peak data from 0.5% ropivacaine injections (with epinephrine 0.27 ± 0.08 μg/ml, without epinephrine 0.32 ± 0.10 μg/ml).

The blood concentration versus time curves after epidural administration for all solutions are shown in Figure 3. Derived pharmacokinetic data after epidural administration of bupivacaine and ropivacaine are given in Table 2. No statistically significant differences were found between the two anesthetics. The

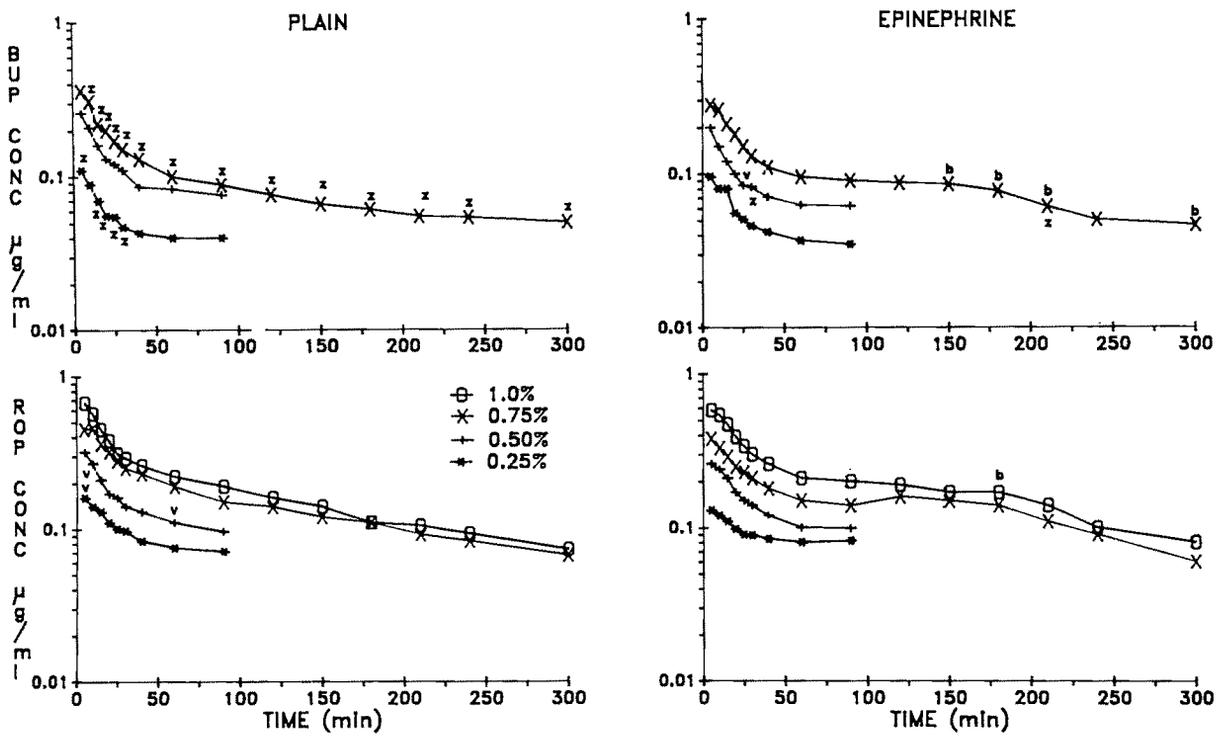

Figure 3. Mean arterial whole blood concentrations of ropivacaine ($n = 6$) and bupivacaine ($n = 5$) after epidural injection of plain and epinephrine containing solutions. Standard deviations have been omitted for clarity. z, $P < 0.05$, bupivacaine < ropivacaine at the same dose; v, $P < 0.05$, plain > epinephrine at the same dose; b, $P < 0.05$, epinephrine > plain at the same dose.

elimination half-life after epidural injection of both drugs was consistently longer than after IV infusion. This is as expected, due to the continued absorption of drug from the epidural space. Clearance of ropivacaine after epidural administration was also consistently less than after IV administration, achieving statistical significance in three of the four treatment groups examined. For bupivacaine, clearance was the same after epidural injection of 0.75% plain solutions and after IV infusion, but clearance was significantly less rapid after epidural injection of 0.75% bupivacaine with epinephrine than after IV infusion. Although peak drug concentrations occurred in blood samples taken 5 or 10 minutes after injection, indicating an absorption rate constant of approximately 0.3 to 1.0 min^{-1}, the mean body residence times of over 200 minutes imply a slow absorption of drug from the epidural space. Mean absorption time (MAT) = $MBRT_{epidural} - MBRT_{IV}$. Mean absorption time for ropivacaine would be approximately 230 minutes and for bupivacaine, 225 minutes.

Discussion

After a 15-minute IV infusion in the dog, ropivacaine has a significantly shorter elimination half-life than does bupivacaine. This is reflected in a mean total body clearance for ropivacaine that is greater than that for bupivacaine. The primary metabolic site for other amide-type local anesthetics is the liver, and if this is also true for ropivacaine, then these data imply that the hepatic extraction of ropivacaine is likely to be greater than the hepatic extraction of bupivacaine in the dog. Bupivacaine has both a greater n-heptane/buffer partition coefficient and a greater propensity toward accumulating in fat and nerve tissue than does ropivacaine (1), suggesting that bupivacaine can accumulate in tissue to a greater extent than ropivacaine. However, in this pharmacokinetic study, both drugs had similar volumes of distribution. Comparison of mean pharmacokinetic data for ropivacaine and other amide local anesthetics indicate that ropivacaine has the shortest elimination half-life, a low steady-state volume of distribution, and is intermediate in terms of total body clearance (Table 3). Total body clearances of the amide local anesthetics are approximately four times greater in dogs than in human (11), but remain in the same order, i.e., etidocaine > lidocaine > mepivacaine > bupivacaine. If ropivacaine follows the same pattern then total body clearance of ropivacaine in humans would be expected to be approximately 0.8 L/min.

Table 3. Pharmacokinetic Data for Amide-Type Local Anesthetics in Dogs after IV Infusion*

	Ropivacaine	Bupivacaine	Mepivacaine	Lidocaine	Etidocaine
$t_{1/2\beta}$ (min)	26	3[illegible]	45	46	60
$V_{D}ss$ (L/kg)	1.1	[illegible]	1.9	2.3	3.4
Cl ($ml \cdot min^{-1} \cdot kg^{-1}$)	41	3[illegible]	39	56	58

*(Arthur—unpublished data.)

There appears to be little difference between bupivacaine and ropivacaine after epidural administration in terms of peak blood concentrations and pharmacokinetic profiles when the same dose is administered. However, if a 1.0% concentration of ropivacaine is required to attain the same duration of anesthesia achieved with 0.75% bupivacaine (3,4), then the resulting blood concentrations of ropivacaine would be greater than those of equianesthetic doses of bupivacaine. The peak arterial concentrations of ropivacaine after the epidural injection of 1.0% solutions are considerably less than those reported to produce convulsions (5) and less than those seen in this study after IV infusion of drug (1.55 to 3.07 μg/ml), at which point minimal objective signs of CNS irritation were observed.

In general, total body clearance values for ropivacaine and bupivacaine after IV infusion were greater than after epidural administration. Total body clearance of local anesthetics is related to hepatic blood flow and thus would be expected to decrease for both ropivacaine and bupivacaine if cardiac output and hepatic blood flow were reduced after epidural blockade, as previously reported after epidural blockade with lidocaine in monkeys (12). This reduction in clearance was seen after epidural injection of all concentrations of ropivacaine with and without epinephrine. The clearance of bupivacaine was reduced when the 0.75% solution with epinephrine was injected epidurally. It is not clear why the clearance of bupivacaine was not reduced after epidural administration of the plain 0.75% solution.

In conclusion, ropivacaine has pharmacokinetic properties after IV infusion in the dog, which indicate that it is more rapidly cleared from the body than is bupivacaine. After epidural injection, the pharmacokinetic profiles of both ropivacaine and bupivacaine are similar and neither drug produced blood concentrations that were close to the toxic threshold. Adding epinephrine (1:200,000) to the epidurally injected solutions had little effect in depressing blood concentrations of either drug.

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Nitrous Oxide:

Cardiovascular Effects in Infants and Small Children During Halothane and Isoflurane Anesthesia

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MURRAY D, FORBES R, MURPHY K, MAHONEY L. Nitrous oxide: cardiovascular effects in infants and small children during halothane and isoflurane anesthesia. Anesth Analg 1988;67:1059–64.

Two-dimensional and pulsed Doppler echocardiography were used to measure cardiovascular function in 31 unmedicated infants and small children. In 15 patients, the cardiovascular effects of equipotent levels of halothane were compared with and without N_2O. In 16 patients, the cardiovascular effects of isoflurane with and without N_2O were compared.

Prior to anesthesia induction, cardiovascular measurements of heart rate (HR), mean blood pressure (MBP), and two-dimensional and pulsed Doppler echocardiography were recorded. The echocardiographic measurements were used to determine cardiac output (CO), stroke volume (SV), ejection fraction (EF), and left ventricular end-diastolic and end-systolic volume (LVEDV and LVESV). Twenty minutes after mask inhalation induction with halothane or isoflurane with N_2O and O_2 (3:2 liters/min), cardiovascular measurements were repeated with end-expired halothane or isoflurane maintained at 0.9 MAC. A third set of cardiovascular data was collected 10 minutes after the discontinuation of N_2O, with inspired isoflurane or halothane levels in O_2 (5 liters/min) increased to maintain 1.5 MAC end-expired levels. Ventilation was controlled throughout the study period and the study was completed before intubation and the start of elective surgery. Heart rate and MBP decreased to similar degrees below awake levels in both patient groups during N_2O with halothane or isoflurane. When N_2O was discontinued and end-expired levels of halothane or isoflurane increased, MBP remained at levels observed during N_2O–O_2 with halothane or isoflurane. Heart rate increased during isoflurane in O_2. Cardiac output decreased significantly and similarly below awake levels during both halothane or isoflurane with and without N_2O. Ejection fraction decreased significantly below awake levels during both N_2O:O_2 and halothane and during halothane in O_2 (30 ± 6 and 32 ± 5%) as well as during isoflurane with and without N_2O (15 ± 9 and 18 ± 7%). Decreases in EF were significantly greater with halothane. In infants and small children, the cardiovascular effects of combining N_2O with halothane or isoflurane were similar to equianesthetic concentrations of halothane and isoflurane in O_2, and may be more profound than suggested by clinical studies in adults.

Key Words: ANESTHESIA—pediatric.
ANESTHETICS, VOLATILE—halothane, isoflurane.
ANESTHETICS, GASES—nitrous oxide.

In adults, when N_2O is substituted for halothane or isoflurane, cardiovascular depression is less than when either agent alone is used to maintain a similar depth of anesthesia (1–6). Because N_2O has relatively minor cardiovascular effects in adults, the addition of N_2O to halothane or isoflurane in infants and small children is assumed to offer similar cardiovascular advantages. In intubated infants, after surgical repair of congenital heart disease, the substitution of 50% N_2O for 50% N_2 in O_2 resulted in a decrease in heart rate, mean blood pressure, and cardiac index, which suggests similar systemic cardiovascular changes to those that occur in adults (7). Few studies in infants and small children are available that measure the cardiovascular effects of N_2O in combination with halothane (8,9) or isoflurane (10), or that compare the cardiovascular effects to equianesthetic concentrations of halothane or isoflurane in oxygen (11,12).

The purpose of this study was to compare the cardiovascular effects of equivalent anesthetic concentrations of halothane or isoflurane with or without

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N_2O. Cardiovascular effects were assessed by blood pressure, heart rate, as well as by pulsed Doppler and two-dimensional echocardiographic derived determinations of ejection fraction, stroke volume, cardiac output, and left ventricular volumes during systole and diastole.

Methods

Thirty-one ASA physical status I infants and small children who required elective surgery were evaluated after the protocol was approved by the hospital's Human Studies Committee. Informed written consent was obtained from the parent(s). The study patients received no premedicants and had fasted for 4–8 hours preoperatively.

Parents accompanied the children to a presurgical care unit where preinduction heart rates, blood pressures by automated oscillotonometry (13) (Omega 1600), two-dimensional echocardiographic measures of left ventricular area and length in systole and diastole, and pulsed Doppler measures of pulmonary artery blood flow velocity were determined for each patient before induction of anesthesia.

The infants and small children were alternately assigned to receive either halothane (n = 15) or isoflurane (n = 16). In the operating room, anesthesia was induced by mask inhalation of halothane or isoflurane in N_2O and O_2 (3:2 1pm) using a semiclosed pediatric circle system. Intraoperative monitoring included precordial stethoscope, mean blood pressure (MBP) (Omega 1600), and heart rate (HR) by ECG. Inspired and expired gas concentrations were measured and recorded using a Perkin-Elmer mass spectrometer.

Following induction of anesthesia and after intravenous access had been achieved, the anesthetic concentration of N_2O was maintained at 60% and the inspired concentration of halothane or isoflurane was adjusted to achieve and maintain 0.9 MAC end-expired levels (MAC adjusted for age) (14,15). With end-expired concentrations constant for at least 5 minutes, two-dimensional and pulsed Doppler echocardiographic data were measured and recorded over 2 minutes (approximately 20 minutes after the start of induction). Following this, N_2O was discontinued and the O_2 flow increased to 5 1pm, the inspired halothane or isoflurane concentrations being increased to achieve stable end-expired levels of 1.5 MAC halothane or isoflurane. Approximately 10 minutes after the discontinuation of N_2O, a third set of cardiovascular data was collected. All cardiovascular measurements were completed prior to tracheal intubation and the start of surgery. Ventilation was controlled throughout the study period (approximately 30 minutes) and IV fluids were withheld.

Ultrasound studies were performed with patients in the supine position using an Ultra Imager 2600 (Biosound, Inc., Indianapolis) mechanical sector scanner with a 5-MHz single-element transducer combined with a 3.5-MHz Doppler interrogation frequency. Short-axis views at the high papillary muscle level and the great vessel level, and apical four chamber views were obtained in each subject. Left ventricular cross-sectional area was measured at the level of the papillary muscles. Left ventricular cavity length was measured in the apical four-chamber view. Pulmonary artery diameter was measured immediately above the level of the semilunar valve.

After the heart and great arteries were imaged a Doppler sample volume was positioned within a 75° sector sampling arch (16). A line on the sample volume cursor documented the flow angle estimated by the ultrasonographer and the velocity was then corrected (velocity/cos θ). The sample volume axial dimension was kept to 3 mm and the lateral width was constant at 1.5 mm. The sample volume was placed in the pulmonary artery immediately above the pulmonic valve and positioning for maximal flow velocity was confirmed by both the intensity of the audio signal and the spectral display of the Doppler shift frequency obtained from fast Fourier transformed spectral analysis. Peak velocity was measured to the top with the most dense signal on the velocity curve and 3 beats/min averaged (16–18). Continuously updated two-dimensional images, Doppler profiles, and simultaneous ECG tracings were displayed on a monitor and recorded on video tape. Selective frozen images were recorded on a strip-chart recorder for measurement. The ultrasonographer who recorded and measured the echocardiographic data was unaware of which anesthetic agent was used to maintain anesthesia.

Left ventricular endocardial enclosed volumes were measured separately at end-diastole and end-systole from two orthogonal planes: parasternal short-axis and apical four-chamber views. Using a microsonic CAD-886 image processing and video quantifications system (Microsonics, Inc., Indianapolis), images were traced along the endocardium utilizing the leading edge method (19,20).

The two-dimensional recordings of left ventricular area at the papillary muscle level and left ventricular length at end-systole and end-diastole were used to calculate left ventricular end-systolic and left ventricular end-diastolic volumes (LVESV and LVEDV) at each study level. Volume was calculated from:

Table 1. Levels of N_2O, Halothane, and Isoflurane

	Concentrations of halothane and isoflurane (vol %)		Ratio of end-expired to inspired	End-expired N_2O level (%)
	End-expired	Inspired		
Halothane				
Level 1	0.95 ± 0.02	1.14 ± 0.04	0.84 ± 0.02	55.8 ± 1.6
Level 2	1.57 ± 0.06	1.84 ± 0.07	0.83 ± 0.02	3.7 ± 0.5
Isoflurane				
Level 1	1.61 ± 0.04	1.84 ± 0.06	0.84 ± 0.01	58.0 ± 1.9
Level 2	2.6 ± 0.06	3.06 ± 0.07	0.80 ± 0.02	4.1 ± 0.6

Table 2. Cardiovascular Data

	Awake	0.9 MAC + 60% N_2O	1.5 MAC
Heart rate (beats/min)			
Halothane	127 ± 5.5	116 ± 6.2*	115 ± 6.0*†
Isoflurane	141 ± 5.0	130 ± 4.6*	140 ± 4.5
Mean blood pressure (mm Hg)			
Halothane	74.3 ± 1.9	59.1 ± 2.1*	55.4 ± 1.5*
Isoflurane	73.5 ± 2.4	59.2 ± 2.5*	57.8 ± 2.6*
Left ventricular end-diastolic volume (ml)			
Halothane	11.9 ± 1.2	13.8 ± 1.1*†	14.0 ± 1.1*†
Isoflurane	9.5 ± 0.6	9.7 ± 0.7	10.2 ± 0.8*
Left ventricular end-systolic volume (ml)			
Halothane	5.6 ± 0.5	7.7 ± 0.6*†	7.4 ± 0.6*†
Isoflurane	4.8 ± 0.4	5.2 ± 0.4	5.2 ± 0.5

*$P < 0.05$ from awake. †$P < 0.05$ from isoflurane.

Volume = ⅝ area × length (18–21).

This formula assumes the ventricular configuration to be a hemisphere cylinder. This measurement correlates with a more sophisticated algorithm calculation (Simpson's Rule) used to measure two-dimensional left ventricular volumes and also with angiographically determined left ventricular volumes in various clinical situations including left ventricular overload (20,21).

The Doppler-determined mean velocity of pulmonary artery blood flow and echocardiographically determined pulmonary artery diameter were used to calculate cardiac output (16,18) using the formula: CO = mean pulmonary blood flow velocity × pulmonary artery area·cos θ^{-1}.

Data were analyzed using a two-factor repeated measures design with the factors being the anesthetic level and agent (halothane or isoflurane). Analysis of variance was performed to determine statistical significance and define interaction. When interaction was present, follow-up comparisons were made. Bonferroni adjustment was used to protect the overall error rates. Statistical significance was accepted at $P < 0.05$. All values are expressed as mean ± SEM.

Results

The age (halothane 11.9 ± 2.3 months, isoflurane 8.9 ± 1.7 months) and weights (halothane 8.8 ± 0.7 kg, isoflurane 7.3 ± 0.6 kg) were not significantly different in the two groups.

Inspired and expired anesthetic gas concentrations, recorded by sampling gases from a tight-fitting Rendell-Baker mask, were measured with a Perkin-Elmer mass spectrometer (Table 1) (see Discussion). Mean end-tidal CO_2 during 0.9 MAC and N_2O and 1.5 MAC in O_2 were similar (30.6 ± 2.1 and 32.1 ± 2.4, respectively).

Heart rate and MBP decreased below awake values during anesthesia with N_2O and 0.9 MAC halothane or isoflurane. The magnitude of the decrease was similar in both groups. After discontinuation of N_2O, HR and MBP remained similar to values measured during N_2O in the patients maintained with 1.5 MAC halothane (Table 2). During 1.5 MAC isoflurane, MBP remained unchanged but HR increased significantly above levels measured during N_2O and 0.9 MAC isoflurane (Table 2).

Cardiac output and stroke volume (SV) decreased similarly and significantly below awake values during

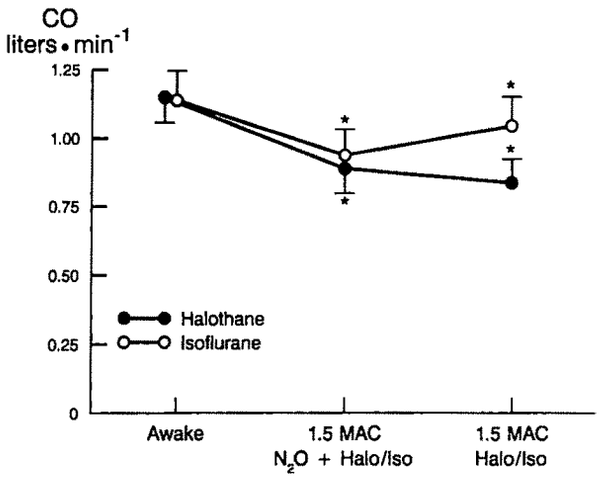

Figure 1. Cardiac output (CO); *$P < 0.05$ from awake; values are expressed as mean ± SEM.

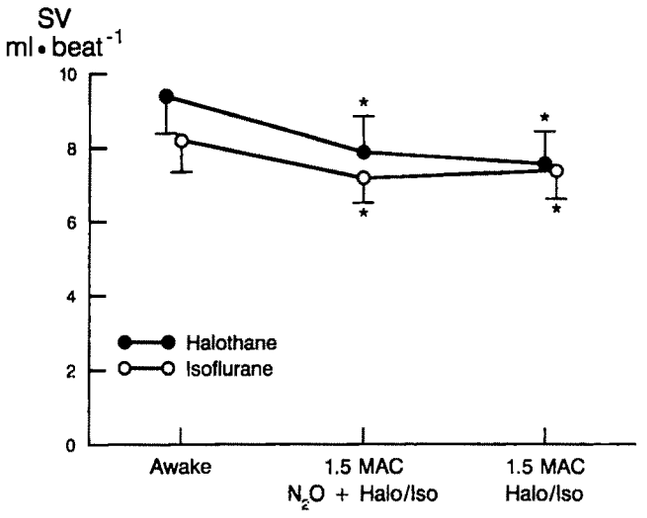

Figure 2. Stroke volume (SV); *$P < 0.05$ from awake; values are expressed as mean ± SEM.

N_2O with halothane or isoflurane anesthesia and with 1.5 MAC halothane and isoflurane anesthesia alone (Figs. 1 and 2). Decreases in CO and SV were similar with both halothane and isoflurane.

Left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) increased similarly and significantly with 0.9 MAC halothane and N_2O and with 1.5 MAC concentrations of halothane in O_2. In the patients given isoflurane, LVEDV increased significantly above awake levels at 1.5 MAC isoflurane in O_2 (Table 2). The increases in LVESV and LVEDV were significantly greater in the infants and small children given halothane.

The decreases in ejection fractions were similar at 0.9 MAC halothane–N_2O and 1.5 MAC halothane–O_2 (30 ± 6 and 32 ± 5%). During isoflurane anesthesia,

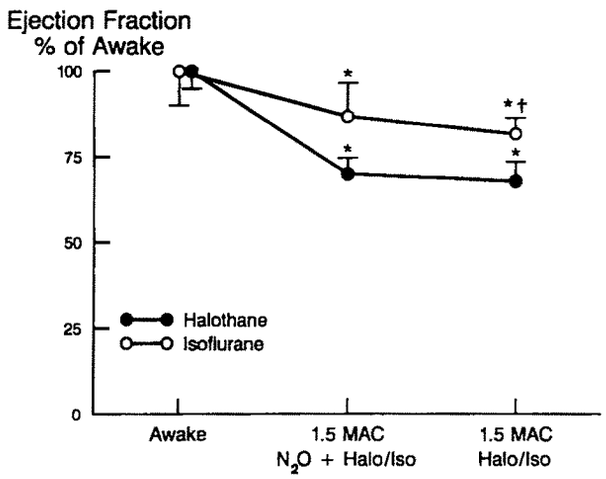

Figure 3. Percentage change in ejection fraction from awake; *$P < 0.05$ from awake; †$P < 0.05$ from halothane; values are expressed as mean ± SEM.

ejection fractions also decreased by similar and significant degrees from awake values during 0.9 MAC and N_2O and 1.5 MAC, 15 ± 9 and 18 ± 7%, respectively. The decrease in ejection fraction was significantly greater in the infants and small children given halothane than in those given isoflurane (Fig. 3).

Discussion

Comparisons of the cardiovascular effects of equianesthetic concentrations of N_2O in combination with halothane and isoflurane and during halothane and isoflurane in O_2 required a number of assumptions about the anesthetic levels we measured. First, we assumed that the concentration of N_2O (i.e., approximately 60%) equalled 0.6 MAC in an infant and small child. Whereas the combination of N_2O with inhalation anesthetics in adults reduces MAC by approximately 1% for each percentage N_2O administered (1,22), the effect of N_2O in reducing MAC is not known in infants and small children. MAC requirements for halothane and isoflurane are greater in infants and small children, and 60% end-tidal N_2O may not approximate 0.6 MAC in pediatric patients, as it does in the adult (1,22).

End-expired CO_2 measurements may underestimate alveolar CO_2 because inspired gas can be entrained during the measurement, particularly when gas samples are not obtained from the trachea (23,24). This problem is magnified in infants and small children with their smaller tidal volumes and rapid respiratory rates. For this reason, ventilation was controlled and the capnogram recorded to assure that

samples of expired gas would better reflect end-tidal anesthetic levels (23,24). While the presence of an alveolar plateau on the capnogram should help minimize the errors in the measurement of end-expired gas by mass spectrometry, the end-expired levels we measured could overestimate actual end-tidal levels if gas from apparatus and anatomic deadspace was entrained during the measurements.

To reflect anesthetic concentrations in the myocardium or brain accurately, end-tidal or alveolar concentrations must be at equilibrium with anesthetic levels in the vessel-rich tissue group (25–27). The time required to achieve equilibrium with either halothane or isoflurane in the vessel-rich tissue group depends on a number of factors, including solubility of the anesthetic as well as tissue blood flow and cardiac output (26). In infants given halothane anesthesia, one time constant of vessel-rich tissue group equilibrium is approximately 2.2 minutes, while with isoflurane, a less soluble anesthetic, the time constant of equilibrium would be expected to be more rapid (27). In this study, with 5-minute periods of stable end-expired concentrations maintained before cardiovascular measurements (approximately two time constants), equilibrium between alveolar and vessel-rich tissue group anesthetic levels may not have been complete. To assist in the assessment of equilibrium between alveolar and vessel-rich anesthetic levels, we recorded inspired and end-expired anesthetic levels during the study. The ratio of end-expired to inspired halothane levels in infants at vessel-rich tissue group equilibrium is estimated to be 0.8 (26,27), which is similar to the levels we recorded during this study (Table 1).

Ten minutes after the discontinuation of N_2O, small but measurable N_2O concentrations (<5%) were still present in end-expired gas which, while expected because vessel-poor tissues would not be at equilibrium with inspired levels, may have influenced the cardiovascular measurements made during 1.5 MAC halothane or isoflurane (26).

Measurements of ventricular volumes with two-dimensional echocardiography correlate with angiographic methods but tend to underestimate angiographic volume measurements. Stroke volume and CO derived from end-diastolic and end-systolic two-dimensional echocardiographic volumes, while used clinically, would also underestimate angiographic SV and CO. For this reason, pulsed Doppler echocardiography was used to determine CO and SV.

Similar to the findings in adult volunteers (2,4), and in prior studies of infants (7,10), we found the use of N_2O alone or with halothane or isoflurane produced significant decreases in HR. The addition of 60% N_2O to halothane or isoflurane did not result in significant differences in MBP, CO, SV, and EF when compared to equianesthetic levels of halothane and isoflurane in O_2. This suggests that use of N_2O in infants and small children in an effort to reduce the concentration of volatile agent may not produce less cardiovascular depression as measured by CO, SV, and EF than occurs when either halothane or isoflurane in oxygen is used to maintain anesthesia.

In adults, signs of sympathetic stimulation that occur on the addition of N_2O are believed to mask the direct cardiovascular depressant effects of N_2O (28,29). In this study, after the discontinuation of N_2O, the $F_{I_{O_2}}$ as well as the inspired halothane or isoflurane levels were increased. Therefore, because of the study design, it was not possible to separate the cardiovascular effects of N_2O from those of halothane and isoflurane or from the effects of increasing $F_{I_{O_2}}$ from 40 to 100%. An increase in $F_{I_{O_2}}$ could decrease pulmonary and systemic vascular resistance and perhaps influence the cardiovascular changes we measured (7). Nonetheless, we anticipated that if N_2O had minimal cardiovascular effects in infants and small children that the combination of N_2O and halothane or isoflurane, when compared to equianesthetic levels of halothane or isoflurane in O_2, would result in less cardiovascular depression. Perhaps direct myocardial depression produced by N_2O is more profound in infants or, alternatively, increases in sympathetic activity that occur in adults during N_2O are less in infants and small children particularly during halothane and isoflurane anesthesia (30).

While changes in MBP, CO, and SV were similar in the halothane and isoflurane groups, infants and small children who received halothane had significantly greater increases in LVESV and LVEDV than did patients who received isoflurane. The differences in LVEDV suggest halothane has a greater effect than isoflurane on preload in infants and small children. Ejection fraction decreased more during halothane than isoflurane anesthesia. It is difficult to conclude whether this represents a difference between halothane and isoflurane in afterload or contractility, because neither cardiovascular determinant could be measured directly by the two-dimensional and pulsed Doppler echocardiographic technique used in this study or in a prior study of infants and small children (12).

In summary, the addition of N_2O to either halothane or isoflurane did not produce less cardiovascular depression when compared to equianesthetic concentrations of halothane or isoflurane in O_2. While N_2O in pediatric anesthesia practice does offer many advantages, including low solubility, absence of

odor, and the ability of high concentrations of N_2O to enhance the rate of increase in alveolar concentrations of the potent inhalation agents, the cardiovascular advantages of adding N_2O to inhalation anesthesia in infants and small children may not be as significant as has been suggested by clinical studies in adults. Further studies are necessary to better define the cardiovascular effects of N_2O in healthy infants and small children.

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Forearm Vascular Tone and Reactivity During Lumbar Epidural Anesthesia

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BARON J-F, PAYEN D, CORIAT P, EDOUARD A, VIARS P. Forearm vascular tone and reactivity during lumbar epidural anesthesia. Anesth Analg 67:1065–70.

Forearm vascular tone and sympathetic reactivity were investigated in ten unpremedicated patients during two levels of epidural sensory blockade, neither of which levels was high enough to block cardiac sympathetic pathways. An 8-MHz pulsed Doppler blood flowmeter was used to determine brachial artery diameter and flow characteristics. Measurements were made before and during sympathetic stimulation induced by a contralateral isometric handgrip. The lower level of sensory blockade (T11) in the absence of sympathetic stimulation was associated with decreases in right atrial pressure, brachial artery diameter (3.9 ± 0.2 vs 4.2 ± 0.2 mm, $P < 0.05$) and brachial blood flow (42 ± 5 vs 66 ± 7 ml·min^{-1}, $p < 0.001$), whereas forearm vascular resistance increased significantly (2.2 ± 0.3 vs 1.5 ± 0.2 mm Hg·ml^{-1}·min^{-1}, $P < 0.01$). Neither heart rate nor mean arterial pressure changed. At the higher level of blockade (T7), right atrial pressure and systemic arterial pressure decreased further without change in heart rate. Brachial artery diameter (3.8 ± 0.2 mm) remained unchanged while brachial blood flow additionally decreased (30 ± 3 ml·min, $P < 0.05$), and forearm vascular resistances further increased (3.0 ± 0.2 mm Hg·ml^{-1}·min^{-1}, $P < 0.01$). Changes in heart rate and in mean arterial pressure associated with isometric exercise were similar before and during epidural anesthesia at both levels of epidural blockade. The increase in forearm vascular resistance induced by contralateral exercise was significantly above control levels during the low level of blockade (0.5 ± 0.1 mm Hg·ml^{-1}·min^{-1}) than at control (0.15 ± 0.1 mm Hg·ml^{-1}·min^{-1}) and higher during the high level of blockade (1.9 ± 0.3 mm Hg·ml^{-1}·min^{-1}). These results indicate that forearm vascular tone and sympathetic reactivity are enhanced during lumbar epidural anesthesia.

ANESTHETICS, LOCAL—bupivacaine. ANESTHETIC TECHNIQUES—epidural. BLOOD PRESSURE, HYPOTENSION—baroreceptor reflexes. REFLEXES—baroreceptor; cardiopulmonary receptors; somatic reflexes.

Hemodynamic changes during lumbar epidural anesthesia result mainly from arteriolar and venous dilation induced by sympathetic blockade. However, the initiation of potential sympathetic compensatory cardiovascular reflexes in sympathetically intact areas may buffer hemodynamic consequences and contribute to limitation of the decrease in arterial pressure. This latter effect has been suggested by forearm blood flow measurements using strain gauge plethysmography (1). Moreover, these data and others suggest a possible increase in vascular reactivity to sympathetic stimuli in sympathetically intact areas during lumbar epidural anesthesia (2). Pulsed Doppler blood flowmetry with a double transducer probe is an accurate noninvasive method for measurements of blood flow in superficial arteries (3). In addition, this technique is sensitive enough to detect changes in large artery diameters in response to physiologic or pharmacologic interventions (4). The present study was designed to measure, at two levels of sympathetic blockade, the vasoactive modification of forearm small and large arteries and to evaluate the forearm vascular reactivity during sympathetic stimulation induced by a contralateral isometric exercise.

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Materials and Methods

Ten patients who gave informed consent (age, 42 ± 9 years, mean ± SD) scheduled for gynecologic or

vascular (varicectomy) surgery, were studied after approval by our Ethics Committee. All were free of cardiac, renal, and hepatic diseases. None had taken any drugs known to influence the cardiovascular or the neuroendocrine systems. Catheters were inserted under local anesthesia (plain bupivacaine) in a peripheral vein, in the lumbar epidural space (L3–4) and in five out of ten patients in the right atrium via a basilic vein. The atrial catheter was connected to a Hewlett-Packard transducer. Position of the atrial catheter was confirmed by pressure waveforms and by characteristic responses to a Valsalva maneuver. ECG (lead II) and atrial pressure were continuously monitored. Throughout the procedure, patients remained in a supine and comfortable position. Lactated Ringer's solution was slowly infused through the peripheral catheter at a rate of 50 ml/hr.

Pulsed Doppler Velocimeter

The zero crosser velocimeter used in this study (Echovar Pulsed Doppler, Alvar Electronics) has, in addition to its pulsed emission, two main characteristics: i) an adjustable ranged-gated time system, and ii) a double transducer probe that provides a bidimensional blood velocity measurement that considerably minimizes the errors introduced by the observation angle between the ultrasonic beam and the vessel axis. Briefly, each transducer acts alternatively as an emitter and receiver. The emitter is a ferro-electric ceramic, used at a frequency of 8 MHz, with an emission duration from 0.5 to 2 μsec and at a pulsed repetition of 15 or 30 KHz. Between the emitted pulses, the transducer operates as a receiver and an electronic gate selects the signals reflected at a given time from the emission. The reception duration can be also selected. Adjustments in time delay and reception duration are made using constant steps of 0.5 μsec. With such a system, it is possible to determine the distance (d) between the red cells in a column of blood and the transducer according to the echographic relation: $d = C/2 \times t$, where C is the ultrasound speed in tissues and t the reception time. The time delay and the duration reception represent the depth and the width of the sample volume along the ultrasound beam axis, respectively. Using this procedure, the diameter of a vessel and the cross-sectional blood flow velocity can be determined.

The double transducer system overcomes the difficulty in measuring the angle between the ultrasonic beam and the vessel axis. The two transducers are set in the probe so that the angle between them is 120°. Probe position is adjusted until two successive velocities, one from each transducer, are equal in absolute value (5). In these conditions the angle between the ultrasonic beam and the vessel axis is 120°/2. Using this method, the error from the determination of the angle is less than 2% (5). The accuracy of the Doppler determinations has been studied with an hydraulic test device using calibrated latex tubes (5): the velocity measured with the pulsed Doppler was within 95% of the known velocity for velocities from 5 to 70 cm/sec and the overestimation of the diameter due to the sample volume size was 0.035 + 0.015 cm.

Brachial Blood Flow Measurements

The pathway of the brachial artery was determined by palpation in the antecubital fossa. An ultrasonic gel was used as a coupling medium between the probe and the skin. The Doppler signals were monitored by a loudspeaker and velocity curves were continuously registered. An approximation of the brachial artery location was first made by adjusting time delay and reception time corresponding to the usual depth and width of the artery. The gate width was then adjusted to obtain Doppler signals from the entire cross-section of the vessel. Probe position was adjusted so that the two velocity curves, successively recorded during ten cardiac cycles, were equal in absolute value. With the probe maintained in correct position using an articulated arm, arterial walls were located by moving a small sample volume (1 μsec) across the vessel lumen by step of 0.5 μsec. The arterial diameter (D) was calculated as

$$D = C/2 \times t \times \sin 60°,$$

where C is the ultrasonic speed in tissue (1540 m/sec) and t the time between the proximal and the distal wall of the vessel. Cross-sectional blood flow velocity was measured with the time delay adjusted to the depth of the proximal wall and reception time was adjusted to the diameter. Mean velocity (VM) was calculated by electronic integration of the velocity curve and was the mean value of ten successive cardiac cycles for each transducer. Brachial blood flow (BBF) was calculated as

$$BBF = \pi D^2/4 \times VM \times 60.$$

Forearm vascular resistances were derived by dividing mean arterial pressure by BBF.

Protocol Study

After a rest period of 30 minutes, basal measurements were performed (CONTROL) and followed by epi-

dural injection of 8 ml 0.5% plain bupivacaine hydrochloride. The second set of measurements was performed 30 minutes after the epidural injection (LOW LEVEL BLOCKADE). Then, a second epidural injection of 8 ml 0.5% plain bupivacaine was performed. Thirty minutes later, the last set of measurements was obtained (HIGH LEVEL BLOCKADE). Each set of measurements included: i) upper extend of epidural anesthesia as determined by loss of cold discrimination tested by applying a compress soaked in ether, ii) heart rate and right atrial pressure, iii) systolic and diastolic arterial pressures measured by means of a mercury sphygmomanometer, iv) brachial artery diameter (D) and sectional mean blood flow velocity (VM) using the pulsed Doppler, and v) forearm skin temperature determined by an electric thermometer. Mean arterial pressure was calculated by adding one-third of the pulse pressure to the diastolic pressure.

All measurements were obtained before and during a contralateral isometric exercise performed at 10% of maximal voluntary contraction and maintained for at least 2 minutes. Isometric exercise was performed with a handgrip dynamometer, and care was taken to ensure that patients performed neither a Valsalva maneuver nor a muscular contraction of the nonexercising arm (6). All measurements were made in the nonexercising arm during the second minute of isometric contraction.

Statistical Analysis

Data were analyzed by a two-way analysis of variance followed, when appropriate, by a multiple range test. $P < 0.05$ was considered statistically significant. A linear regression analysis was performed between changes in arterial diameter and changes in arterial pressure and between changes in right atrial pressure induced by lumbar epidural anesthesia and changes in forearm vascular resistances observed during isometric exercise. All values were expressed as mean ± SEM.

Results

Low Level of Blockade

Thirty minutes after the first epidural injection of 8 ml plain bupivacaine, the superior level of blockade ranged from T12 to T9 (mean T11). At this time, right atrial pressure decreased significantly without significant changes in arterial pressure or heart rate (Table 1). Brachial artery diameter, mean velocity, and blood flow decreased significantly below control values (Table 1). No relation was found between changes in brachial artery diameter and changes in systolic arterial pressure ($r = 0.20$). Forearm skin temperature decreased significantly and forearm vascular resistances increased significantly (Table 1).

Table 1. Hemodynamic Effects of Low (T11) and High (T7) Levels of Epidural Blockade

		Epidural Anesthesia	
	Control	Low level	High level
SAP (mm Hg)	119 ± 4	113 ± 4	109 ± 4†
DAP (mm Hg)	71 ± 2	68 ± 2	64 ± 2†,§
MAP (mm Hg)	87 ± 3	83 ± 2	79 ± 2†
HR (beats/min)	73 ± 3	71 ± 4	73 ± 3
RAP (min Hg)	4.6 ± 0.7	3.4 ± 0.4*	1.4 ± 0.4†,§
BA diameter (min)	4.2 ± 0.2	3.9 ± 0.2†	3.8 ± 0.2†
VM (cm/sec)	7.8 ± 0.6	5.8 ± 0.5†	4.5 ± 0.3‡,§
BBF (ml/min)	66 ± 7	42 ± 5‡	30 ± 3†,§
FVR (ml/min/mm Hg)	1.5 ± 0.2	2.2 ± 0.3†	3.0 ± 0.2‡, ‖
Skin T° (°C)	30°6 ± 0°7	29°8 ± 0°7‡	28°9 ± 0°7‡,§

Significant difference from control value: *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$.

Significant difference between high and low level: §$P < 0.05$, ‖ $P < 0.01$.

Abbreviations: (SAP) systolic arterial pressure; (DAP) diastolic arterial pressure; (MAP) mean arterial pressure; (HR) heart rate, (RAP) right atrial pressure; (BA) brachial artery diameter; (VM) mean blood flow velocity; (BBF) mean brachial blood flow; (FVR) forearm vascular resistances, and (Skin T°) skin temperature.

High Level of Blockade

Thirty minutes after the second epidural injection of bupivacaine the upper level of anesthesia was significantly higher ($P < 0.01$) and ranged from T9 to T6 (mean T7). Right atrial pressure decreased significantly more and was at this time associated with significant decreases in systolic, diastolic, and mean arterial pressures (Table 1). There was no change in heart rate. No additional decreases in brachial artery diameter was observed, while mean velocity and blood flow significantly decreased during this higher level of blockade (Table 1). Forearm vascular resistances increased and forearm skin temperature decreased when compared with both control and low epidural anesthesia blockade levels (Table 1).

Isometric Exercise

During the two levels of blockade, changes in heart rate and in mean arterial pressure induced by isometric exercise were not significantly different from con-

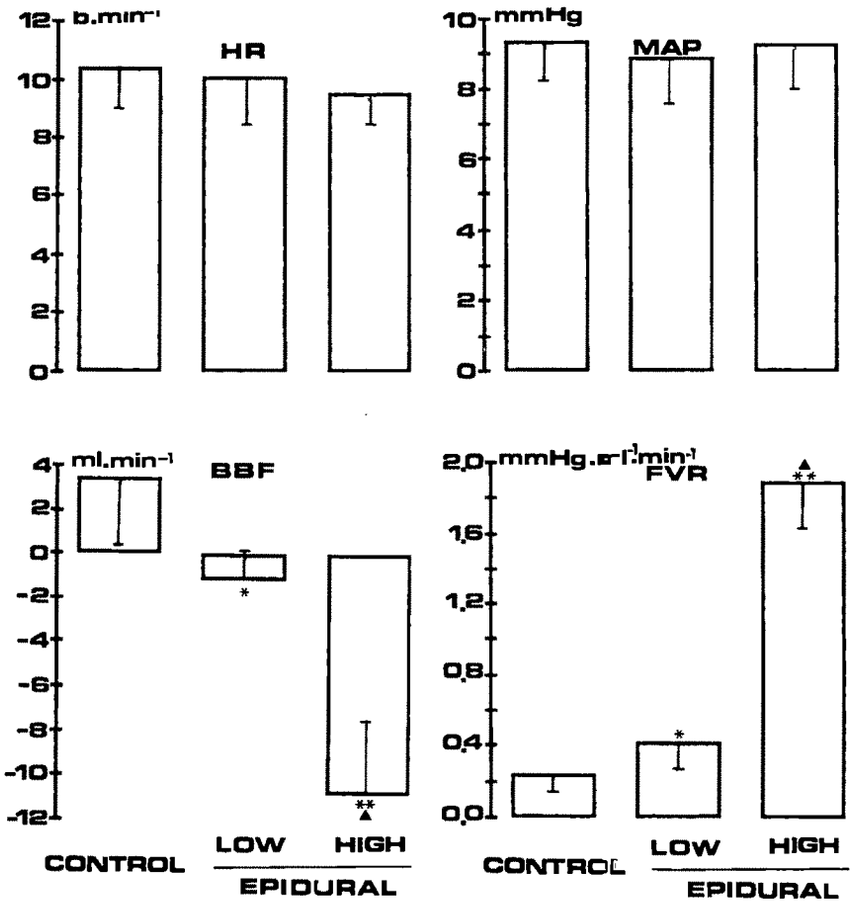

Figure 1. Changes in heart rate (HR), mean arterial pressure (MAP), brachial blood flow (BBF), and in forearm vascular resistances (FVR) induced by contralateral isometric exercise at 10% of maximal voluntary contraction during control, low, and high levels of epidural blockade. Significant difference from control: $^{*}P < 0.05$; $^{**}P < 0.01$. Significant difference between high and low level: $P < 0.01$.

trol values (Fig. 1). However, brachial blood flow, which increased slightly during isometric exercise at control, decreased significantly with the low level of blockade. As a result, the increase in forearm vascular resistance induced by exercise was significantly greater with low level of blockade than at control (Fig. 1). During high lumbar epidural anesthesia, changes in brachial blood flow and in forearm vascular resistances induced by isometric exercise were significantly more pronounced than during the low level of blockade. Linear regression analysis between changes in right atrial pressure due to lumbar epidural anesthesia and changes in forearm vascular resistances during isometric exercise gave a correlation coefficient of 0.91, $P < 0.01$ (Fig. 2).

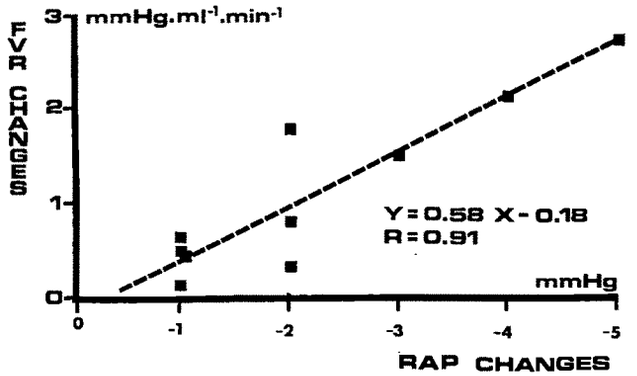

Figure 2. Linear regression analysis between changes in right atrial pressure induced by lumbar epidural anesthesia and changes in forearm vascular resistances induced by isometric exercise during lumbar epidural anesthesia.

Discussion

We undertook this study to: i) quantify the reflex musculocutaneous vasoconstriction in sympathetically intact areas during lumbar epidural anesthesia; ii) evaluate whether this adaptation depends on the level of blockade and; iii) determine if sympathetic hypersensitivity exists in the sympathetically intact area.

The pulsed Doppler method used here has been previously validated (5) and used for measurements in the brachial artery (4) and other superficial vessels (7,8). The resolution of this apparatus is 0.1 KHz (1.9 cm/sec), and the recurrence frequency is 32.4 KHz. Because of the influence of diameter measurements

on flow calculations, it might be useful to mention previous validations. With the same equipment and the same double transducer probe, Simon et al. (4) demonstrated, in an in vitro model, the accuracy of pulsed Doppler diameter measurements, as compared with diameters of calibrated tubes. The intercept of the linear regression was 0.35 mm. Because the smallest value measured of diameter measured in our study was 2.8 mm, the maximal error was 12.5%. Even if the values we measured were false, the impact on our study would be negligible, assuming that error is constant, because we used exactly the same procedure at each step in our protocol. The error due to the incidence angle variation could be large for Θ value used (0 to 60°). The double transducer probe largely minimizes this error (3–5). We took the greatest care at this time to ensure that the probe was in proper position. Values of brachial artery diameter, blood velocity, and flow measured using this method are in agreement with anatomic and physiologic findings (3). Finally the pulsed Doppler technique has several advantages compared with strain gauge plethysmography, which needs venous occlusion. The cuff pressure used for plethysmographic blood flow measurement collapses deep veins and/or arteries and thus might induce a relative hyperemia and/or activation of local reflexes (9).

Using this Doppler method, vasoconstriction involving both small and large arteries was shown during lumbar epidural anesthesia to occur in unblocked musculocutaneous areas. The low level of blockade induced few hemodynamic changes. The slight decrease in right atrial pressure that we observed may be related to a decrease in venous return (10) and in cardiopulmonary blood volume (11). During the high level of blockade the absence of reflex tachycardia in relation to the decrease in arterial pressure may be attributed to enhancement of cardiac vagal tone (12). The decrease in brachial artery diameter we observed was small and approached the limit of sensitivity of the method. This decrease in diameter was independent of the decrease in pressure, (4) and thus, cannot be explained by a mechanical phenomenon, as suggested by the lack of correlation between brachial artery diameter and systolic blood pressure. Increase in forearm vascular resistance and decrease in forearm cutaneous temperature reflected a muscular and cutaneous arteriolar constriction induced in the sympathetically intact area by lumbar epidural anesthesia. Several mechanisms may have contributed to this vasoconstriction: arterial baroreflex adaptation, activation of low pressure cardioreceptors, thermal regulation, and local anesthetic plasma levels.

Sinoaortic baroreceptors seem to play a minor role in the control of musculocutaneous vasomotor activity when compared with low pressure cardiopulmonary receptors (13). Moreover, the vasoconstriction accompanying the low level of epidural blockade was associated only with a decrease in right atrial pressure without changes in arterial pressure. This suggests that low pressure cardiopulmonary receptors may have mediated the forearm vasoconstrictor response (13,14). The influence of forearm cutaneous thermal receptors on reflex vasoconstrictor responses observed in our study may not be excluded although brachial blood flow is influenced less by thermal regulation than is radial blood flow (15). Finally, bupivacaine plasma levels may induce a dose-dependent vasoconstriction on muscular arterioles (16).

In addition to the forearm vasoconstriction observed at rest, the present study shows an increased vascular response to sympathetic stimulus. Activation of somatic receptors by a calibrated exercise triggers excitatory reflex responses as a result of increased adrenergic discharge (17). An interaction between somatic reflexes and cardiopulmonary low pressure reflexes may explain this increased vasoconstrictor response induced by isometric exercise (6,18). This has been demonstrated in humans, using lower body negative pressure to decrease venous return and unload cardiopulmonary receptors (6,18). This hypothesis is also supported by the relation found between changes in forearm vascular resistances induced by isometric exercise and decreases in right atrial pressure during epidural blockade. Again, the influence of either the arterial baroreflexes or thermal regulation or bupivacaine plasma levels cannot be excluded.

The vasoconstriction involving large and small arteries in unblocked musculocutaneous areas seen in the present study during epidural anesthesia has been previously reported using strain gauge plethysmography (1) or scintigraphic regional blood volume measurements (11). Similar adaptations have also been described during spinal anesthesia using Laser-Doppler and skin temperature measurements (20). However, a recent study using a very sensitive thermographic method showed a partial sympathetic blockade involving at least six spinal segments above the level of analgesia during spinal anesthesia (19). However, in view of our results and those of Arndt et al. (11), such an extended area of differential blockade is unlikely during epidural anesthesia. Furthermore, the increased sympathetic reactivity in those unblocked areas that we observed explain why drugs such as ketamine that are known to centrally increase

sympathetic tone (21) produce the same increase in arterial pressure in the presence and absence of epidural anesthesia (2).

In conclusion, lumbar epidural anesthesia without high sympathetic blockade enhances arterial vascular tone and reactivity in sympathetically intact areas. These vascular adaptations to a limited sympathetic blockade seem to be mainly due to the removal of the tonic inhibition of low pressure cardiopulmonary receptors. These findings may explain why lumbar epidural anesthesia in supine position induces but few hemodynamic changes in normovolemic patients.

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Respiratory Effects of Epidural and Subcutaneous Morphine, Meperidine, Fentanyl and Sufentanil in the Rat

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VAN DEN HOOGEN RHWM, BERVOETS KJW, COLPAERT FC. Respiratory effects of epidural and subcutaneous morphine, meperidine, fentanyl, and sufentanil in the rat. Anesth Analg 1988;67:1071–8.

This study compared the respiratory effects of subcutaneous and epidural morphine, meperidine, fentanyl, and sufentanil in rats breathing air or 8% CO_2 in air. A whole body plethysmographic technique was used to measure minute volumes of breathing. The ED_{50}s of subcutaneously injected morphine, meperidine, fentanyl, and sufentanil in depressing the minute volume response to 8% CO_2 in air were 2300 μg/kg, 8800 μg/kg, 20 μg/kg, and 2.3 μg/kg, respectively. These doses were nearly the same as the subcutaneous ED_{50}s of these compounds in producing analgesia, found in an earlier study. Roughly equianalgesic doses of the four opiates after epidural injection, however, failed to cause any detectable respiratory effect. Fourfold greater doses increased significantly the incidence of low minute volumes with fentanyl and sufentanil, but soon after epidural injection, i.e., at the time that analgesia was produced. None of the epidurally injected opiates had a significant delayed effect on respiration. However, one of the seven rats treated epidurally with the higher dose of morphine developed depression of the minute volume response to 8% CO_2 in air as late as 7 hours after the injection. We conclude that epidural injection, in contrast to subcutaneous injection, of analgesic doses of morphine, meperidine, fentanyl, and sufentanil produces no significant respiratory effects.

Key Words: ANALGESICS—morphine, meperidine, fentanyl, sufentanil. ANESTHETIC TECHNIQUES, EPIDURAL—narcotics. VENTILATION—carbon dioxide response.

Systemically administered opiates exert their analgesic effects by binding with opiate receptors both in the brain and in the spinal cord (1,2). Opiate receptors, however, also occur with high density in medullary areas involved in respiratory control (3). An interaction of opiates with these receptors is responsible for the potentially fatal side-effect of opiates: respiratory depression (4).

After intrathecal or epidural administration in man, opiates produce selective, regional analgesia and side-effects including pruritus, urinary retention, and respiratory depression (5–8). Respiratory depression with spinal opiates, however, has a relatively low incidence and occurs at highly variable and, on occasion, surprisingly late times after injection (9–14). Respiratory depression early after epidural injection is probably caused by vascular uptake from the epidural space and transport to the brain. Late depression is thought (8,10) to result from diffusion throughout the cerebrospinal fluid (CSF) to the brain stem. The pharmacologic effects and side-effects of epidural opiates presumably depend on the lipid solubility (8,10) and dural permeability (15), but systematic data on the fate and actions of epidural opiates are lacking (8). In a previous study (16), we examined the analgesic and some other pharmacologic actions of morphine, meperidine, fentanyl, and sufentanil after subcutaneous and epidural injection in rats.

This study reports on the respiratory effects of the same compounds under similar conditions of drug administration. A first series of experiments established dose–response curves for morphine, meperidine, fentanyl, and sufentanil in affecting ventilation at the time of their peak analgesic effect after subcutaneous injection. A second series of experiments measured respiration repeatedly for up to 8 hours

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after epidural injection of selected doses of the same opiates.

Materials and Methods

Animals

Male Wistar rats weighing 250 ± 20 g were used. The animals arrived from the breeding quarters immediately before epidural catheterization or subcutaneous injection. Rats were used only once. The laboratory was air-conditioned (21 ± 1°C; relative humidity 65 ± 5%).

Epidural Catheterization

The catheter implantation technique used here is a slight modification of the technique described in detail elsewhere (17). Briefly, under Thalamonal (Innovar; 2.5 mg droperidol and 0.05 mg fentanyl per ml; 1.5 ml per rat) and pentobarbital (3.5 mg/kg) anesthesia a polyethylene catheter (PE-10; ID 0.28 mm) was introduced into the lumbar epidural space over a length of 0.5 cm cephalad via a hole drilled in the fourth lumbar vertebra.

The catheter was fixed to the vertebra with dental acrylic and the loose end was subcutaneously tunneled towards the neck. After being flushed with sterile saline the catheter was occluded with a metal stopper. Animals were given 1 week to recover from surgery. During this time they were housed individually in standard rodent cages and had free access to food and tap water. Animals showing signs of neurological damage or infection at the site of the operation were excluded from experiments. All animals were killed after the experiments and the position of the catheter tip was checked on autopsy. Only the results of those animals in which the catheter tip was in the lumbar epidural space and in which no epidural fibrinous tissue surrounding the catheter or perforation of the dura was found were used for data analysis. The procedure of epidural administration has been detailed elsewhere (17); 20 μl of either drug solution or saline was injected in 1-μl steps, within about 60 seconds.

Ventilation

Tidal volume and frequency of breathing were determined by means of whole body plethysmography. The apparatus and methods used for this purpose have been described in detail elsewhere (18). Briefly, each rat was placed in a 7/L plexiglass chamber that was flushed with humidified air. After an adaptation period of about 60 minutes, animals were taken out of the plethysmograph to receive pharmacological treatment and then returned to the plethysmograph. The animal chamber was flushed for 10 minutes with air or 8% CO_2 in air saturated with water vapor. Earlier experiments (18) indicated that 8% CO_2 in the inspirated air produced a reliable stimulation of ventilation in untreated rats. For ventilatory measurements, the plethysmograph was made airtight by closing the inlets and outlets of the chambers. In each rat at least three measurements of ventilation were made, each consisting of six breaths. Ventilation was measured by measuring the pressure differences between the animal chamber and a reference chamber of identical size and construction. In the course of each measurement, 0.25 ml of air was extracted from and later rapidly reinjected into the animal chamber for the purpose of calibration. Tidal volume (V_T in ml) was computed as described earlier (18). Respiratory frequency (f; breaths per min) was read directly from the pressure record. V_T and f were computed from each sample. Minute volume ($\dot{V}_E$; $ml \cdot min^{-1} \cdot 100\ g^{-1}$) was determined using the equation

$$\dot{V}_E = \frac{V_T \times f \times 100}{bw}$$

in which body weight (bw) is expressed in grams. The sample yielding the median $\dot{V}_E$ was used for data analysis.

Subcutaneous Experiments

Rats were injected with doses of morphine (0.63–160 mg/kg), meperidine (2.5–160 mg/kg), fentanyl (0.01–0.63 mg/kg), sufentanil (0.00063–0.04 mg/kg) (n = 5 per dose), or saline (n = 21). Each animal was exposed in a random sequence to air and 8% CO_2 in air, separated by an interval of at least 10 minutes. Measurements were carried out at the time of the peak analgesic effect after subcutaneous injection (16), i.e., 60 minutes with morphine, 45 minutes with meperidine, and 30 minutes with fentanyl and sufentanil. Control experiments with saline (n = 5, 6, and 10 respectively), were performed simultaneously. As the control data at these different intervals did not differ, they were pooled for the purpose of data presentation and analyses. All experiments were carried out between noon and 6:00 PM.

Epidural Experiments

Rats (n = 7 in each group) were injected with morphine (40–160 μg), meperidine (640–2500 μg), fentanyl (10–40 μg) sufentanil (2.5–10 μg) or saline (n = 23). Animals were exposed to 8% CO_2 in air for at least 10 minutes before ventilation was measured 15 and 30 minutes after injection and then every half an hour for up to 8 hours. Ventilatory data in the two control groups that were run simultaneously with the low and high dosage groups did not differ significantly (two-tailed $P > 0.05$; Mann–Whitney U-test) (19) and were pooled for data analyses. Experiments were carried out between 8:00 AM and 6:00 PM.

Drugs

Morphine HCl, meperidine HCl, fentanyl citrate, and sufentanil citrate were freshly prepared as aqueous solutions. Injections were made in a volume of 1 ml/100 g body weight in the subcutaneous experiments and in a volume of 20 μl per rat in the epidural experiments. The selection of doses was based on earlier experiments (16). Doses of morphine and meperidine are expressed as the salt; doses of fentanyl and sufentanil refer to the base.

Statistics

Within group analyses utilized the Wilcoxon matched pairs and between group analyses the Mann–Whitney U-test (19). The slopes of regression lines were compared using the methods described by Davies (20). The level of significance was set at $P \leq 0.05$. ED_{50} values were computed by probit analysis (21).

Results

Subcutaneous Experiments

Rats breathing air. After subcutaneous injection of morphine, meperidine, fentanyl, and sufentanil, minute volumes of rats breathing air decreased dose-dependently (Fig. 1). The slopes of the dose–response curves of the four opiates, −12 with morphine and meperidine, and −22 with fentanyl and sufentanil, did not differ significantly (20).

Rats breathing 8% CO_2 in air. The opiates also decreased $\dot{V}E$ while rats breathed 8% CO_2 in air. With each of the four compounds the slope of the dose–response curve in depressing $\dot{V}E$ was steeper on exposure to CO_2 than on exposure to air; P values were < 0.001, < 0.005, < 0.05 and < 0.05 with morphine, meperidine, fentanyl, and sufentanil, respectively.

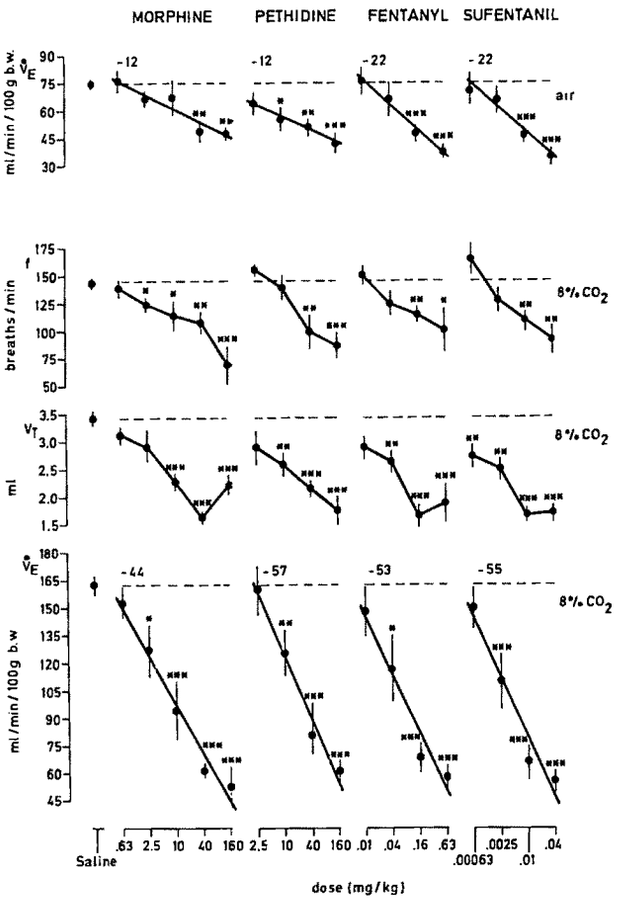

Figure 1. Minute volumes ($\dot{V}E$), computed from frequency of ventilation (f) and tidal volume (VT), after subcutaneously administered doses of morphine, meperidine, fentanyl, and sufentanil in rats breathing air or 8% CO_2 in air. Data points represent the mean ± 1 SEM and are fitted by regression lines of which slopes are indicated. Asterisks refer to the one-tailed probability of the difference with control data to be <0.05 (*), <0.01 (**) or <0.005 (***) (Mann–Whitney U-test) (19).

The depression of the minute volume response to 8% CO_2 resulted from an effect on both frequency and tidal volume. All four drugs depressed frequency in a dose-dependent manner. The compounds also decreased tidal volume, but the highest dose that was tested with morphine, fentanyl, and sufentanil depressed VT less than the dose that was four times lower. A similar pattern of opiate effects on tidal volume has also been obtained in an earlier study on morphine (18).

ED_{50} values. Because one of the 21 subcutaneously treated control animals (i.e., 4.8%) had a $\dot{V}E < 127$ ml · min^{-1} · 100 g^{-1} on exposure to 8% CO_2, this value

Table 1. Respiratory and Analgesic Effects of Morphine, Meperidine, Fentanyl, and Sufentanil after Epidural and Subcutaneous Injection in Rats*

Row	Index	Morphine	Meperidine	Fentanyl	Sufentanil
			Subcutaneous		
A_1	Ventilation ID_{25} (μg/kg)	2900	11,000	30	1.6
B	Analgesia ED_{50} (μg/kg)	1810(920–3570)	6380(3310–12,290)	12(6.7–20)	1.3(0.73–2.3)
C_1	Ratio A_1/B_1	1.6	1.7	2.5	1.2
D_1	Ventilation ED_{50} (μg/kg)	2300(650–12,280)	8800(2680–27,500)	20(6.7–60)	2.3(1.1–4.9)
			Epidural		
A_2	Ventilation ID_{25} (μg/kg)	4400	15,200	56	4.6
B_2	Analgesia ED_{50} (μg/kg)	33(19–57)	374(217–644)	3.2(1.8–5.4)	0.40(0.23–0.69)
C_2	Ratio A_2/B_2	133	41	18	12
			Route differences		
E	Ratio A_2/A_1	1.5	1.4	1.9	2.9
F	Ratio B_1/B_2	55	17	1.8	3.3

*Respiratory data were obtained in this study; analgesic data are from a parallel study (16). Ranges given in parentheses.

was chosen as a criterion of subcutaneous drug activity. ED_{50} values (and 95% confidence limits) were computed (21) according to this criterion, and are given in Table 1. Sufentanil had an ED_{50} of 2.3 (1.1–4.9) μg/kg, and was 9-, 1000-, and 3826-fold more potent in depressing $\dot{V}_E$ than fentanyl, morphine, and meperidine, respectively. Note that the respiratory ED_{50} values of the four subcutaneous opiates differed from their analgesic ED_{50} values by no more than a factor of about 1.5 (i.e., from 1.3 to 1.8; Table 1) indicating that respiratory and analgesic effects occurred at virtually the same dose on subcutaneous injection of the compounds.

25% inhibition. The subcutaneous doses of the opiates that reduced control $\dot{V}_E$ 25% (ID_{25}) in rats breathing 8% CO_2 were computed (Table 1).

Epidural Experiments

Group data. The $\dot{V}_E$ of saline control animals exposed to 8% CO_2 averaged about 210 ml · min^{-1} · 100 g^{-1} immediately upon epidural injection (Fig. 2). Afterwards, $\dot{V}_E$ decreased significantly to about 150 ml · min^{-1} · 100 g^{-1} five hours after injection, and then slightly increased again (not significant).

Sufentanil, 0.63 μg/rat, decreased $\dot{V}_E$ to an average of 180 ml·min^{-1} · 100 g^{-1} 15 minutes after injection, but the difference with control data was not significant (one-tailed, $P > 0.05$). None of the other drugs showed any apparent effect on $\dot{V}_E$ at the lower dose. The higher dose of each of the four opiates decreased the $\dot{V}_E$ 15 minutes after injection, but only with 2.5 μg of sufentanil was the difference with control data significant (one-tailed, $P < 0.05$) (Fig. 2).

Individual data points. The data analysis given in Figure 2 essentially consists of comparisons of groups of data points and leaves it undetermined whether the opiates produced a depression of $\dot{V}_E$ in individual animals. Data were therefore also analyzed in terms of the occurrence of aberrant $\dot{V}_E$ data points. Two criteria of $\dot{V}_E$ were defined on the basis of the control data. Firstly, $\dot{V}_E$-values in drug-treated rats lower than 125 ml · min^{-1} · 100 g^{-1} will be taken as "low $\dot{V}_E$'s" with a $P < 0.05$, as 4.9% of the 391 $\dot{V}_E$ data points ($n = 23$; 17 time intervals) that were obtained from control rats, had values under 125 units. Secondly, drug-treated rats with a $\dot{V}_E$ lower than 89 ml · min^{-1} · 100 g^{-1} will be considered as in "true depression" with a $P < 0.005$, as 89 units was the lowest control $\dot{V}_E$ measured.

The incidence of "low minute volumes" (Table 2) is reported separately for the early and late episodes of time after injection; the early episode was defined as the period of time during which the compounds produced analgesia in an earlier study (16). The late episode was defined as the time between the end of the early episode, and the end of the 8-hour interval after injection. Analysis of the data reveals that 10 μg of fentanyl and 2.5 μg of sufentanil reliably increased the incidence of "low minute volumes" early upon their injection. None of the pharmacologic treatments caused any significant effect late after injection (Table 2). Greater variability after drug treatments than after saline injection may merely reflect smaller sample sizes ($n = 7$ versus 23 per time interval).

A "true depression" with a $\dot{V}_E$ of 86 units occurred

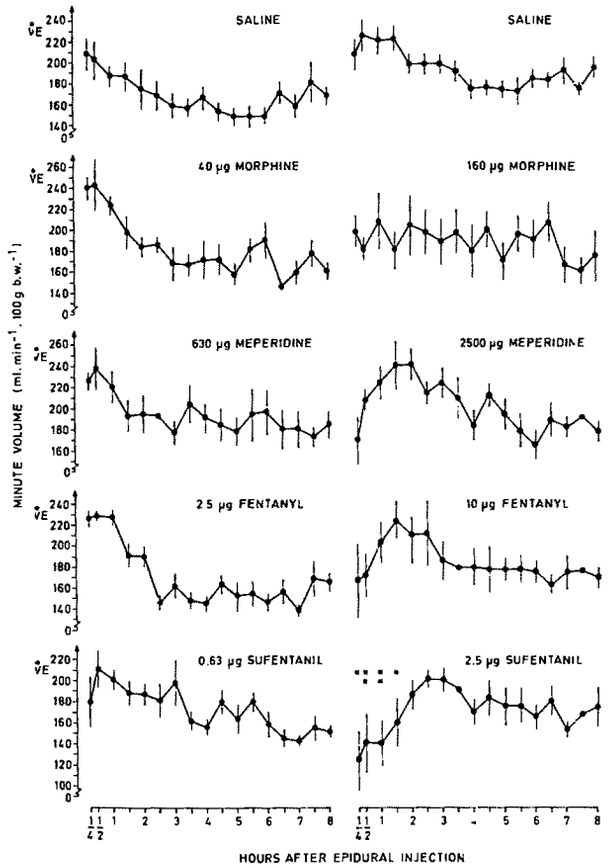

Figure 2. Mean minute volumes (± 1 SEM) at stated time intervals after epidurally administered doses of morphine, meperidine, fentanyl, and sufentanil, in rats that breathed 8% CO_2 in air. Asterisks indicate the one-tailed probability of the difference with saline control data to be <0.05 (*) or <0.01 (**) (Mann–Whitney *U*-test) (19).

once in one rat 7 hours after epidural injection of 160 µg of morphine. Early after injection, a "true depression" also occurred in two of seven animals treated with 10 µg fentanyl and in four of seven animals treated with 2.5 µg of sufentanil.

25% Inhibition. The doses of the opiates that reduced control $\dot{V}_E$ 25% (ID_{25}) 15 minutes after epidural injection in rats breathing 8% CO_2 in air were computed (Table 1).

Further Data Analyses

Comparison of epidural and subcutaneous data reveals that the respiratory ID_{25} values were essentially similar with the epidural and the subcutaneous route (Table 1, row E). Data obtained in an earlier parallel study (16) on analgesia indicated, in contrast, that all four compounds were more potent in producing analgesia after epidural than after subcutaneous injection (row F). As a result, the ratio of respiratory to analgesic doses, which was about 1.5 with all four compounds after subcutaneous injection (row C_1), was greater after epidural injection (row C_2). The epidural ratio varied from 12 with sufentanil, to 133 with morphine. This ratio correlates (Spearman Rank Correlation Coefficient (19): $r_s = -1.0$; $P < 0.05$) with the octanol-to-water partition coefficient (8) of the four compounds.

In none of the epidural studies with opiates was it likely that hypoxemia was produced; at no point was the $\dot{V}_E$ lower than about the 75 ml · min^{-1} · 100 g^{-1} level at which control rats breathed air (Fig. 1).

Discussion

The present experiments examined the ventilatory effects of subcutaneous and epidural injection of varying doses of morphine, meperidine, fentanyl, and sufentanil in rats. After subcutaneous injection, the opiates depressed minute ventilation in rats breathing both air and 8% CO_2 in air. In all cases depression of $\dot{V}_E$ was proportional to dose, and the slopes of the dose–response curve of the four compounds were parallel within statistical limits. The depressant effects of the opiates had the following characteristics. Firstly, the rank order of potency of the four compounds in depressing $\dot{V}_E$ (i.e., sufentanil > fentanyl > morphine > meperidine; Table 1) was the same as that (16) in producing analgesia. This finding confirms informal observations (23) that the respiratory and analgesic potencies of typical opiate analgesics are related. This relationship probably reflects the fact that both pharmacologic actions, analgesia and respiratory depression originate in the central nervous system (CNS), so that the rate of penetration into the CNS after subcutaneous injection co-determines the doses at which these actions occur. Secondly, the doses at which ventilatory and analgesic effects occurred were virtually the same; with all four compounds the analgesic ED_{50} falls within the 95% confidence limits of the ventilatory ED_{50} (Table 1). This finding is consistent with a recent dose–response study of the analgesic and respiratory effects of intravenous fentanyl in dogs (24) and with data in humans (25) that respiratory depression occurs with the doses of systemically administered opiates required to produce analgesia. Thirdly, the slopes of the dose–response curves of the opiates in depressing $\dot{V}_E$ while rats breathed 8% CO_2 were consistently steeper than those obtained while rats breathed air (Fig. 1). However, this finding should

Table 2. Incidence of Low Minute Volumes Early and Late after Epidural Injection of Morphine, Meperidine, Fentanyl, and Sufentanil in Rats Breathing 8% CO_2 in Air

Drug	Dose (μg/rat)	Episodes of time after epidural injection (min)		Incidence (in %) of $\dot{V}_E < 125$ ml·min^{-1}·100 g^{-1}			
				Saline control		Drug-treated	
		Early	Late	Early	Late	Early	Late
Morphine							
	40	15–30	60–480	2.5 (23,2)	5.0 (23,15)	7.1 (7,2)	4.8 (7,15)
	160	15–150	180–480	4.5 (23,6)	5.3 (23,11)	4.8 (7,6)	7.8 (7,11)
Meperidine							
	630	15–30	60–480	2.5 (23,2)	5.0 (23,15)	0.0 (7,2)	4.8 (7,15)
	2500	15–60	90–480	1.6 (23,3)	5.4 (23,14)	9.5 (7,3)	2.0 (7,14)
Fentanyl							
	2.5	15–30	60–480	2.5 (23,2)	5.0 (23,15)	0.0 (7,2)	9.5 (7,15)
	10	15–60	90–480	1.6 (23,3)	5.4 (23,14)	14 (7,3)†	3.1 (7,14)
Sufentanil							
	0.63	15–30	60–480	2.5 (23,2)	5.0 (23,15)	14 (7,2)	4.8 (7,15)
	2.5	15–90	120–480	2.3 (23,4)	5.4 (23,13)	46 (7,4)‡	7.7 (7,13)

The number of animals and the number of time intervals on which the incidence indicated is based, is given in parentheses. Comparison between incidences in drug and saline-treated animals were made by means of the Fisher exact probability test (19).
†One-tailed $P < 0.05$.
‡One-tailed $P < 0.001$.

not obscure the fact that the ranges of dose at which ventilatory effects occurred were essentially the same with the two inspirates.

The epidural injection of roughly equianalgesic doses (16) of morphine, meperidine, fentanyl, and sufentanil failed to cause any detectable ventilatory effect (Fig. 2; left panel). A four times greater dose decreased the $\dot{V}_E$ response to the CO_2 challenge. Analysis of group data (Fig. 2) indicated this decrease to be statistically significant with sufentanil, but not with any of the other opiates. Analysis of individual data points (Table 2) revealed that the higher dose of both sufentanil and fentanyl reliably increased the incidence of "low minute volumes" early upon injection, i.e., at the time (16) that analgesia was produced. Like the analgesic effects determined in an earlier study (23), these ventilatory effects upon injection are related to the lipid solubility of the compounds. None of the opiate treatments had a significant late effect on ventilation, except that one rat showed a "true depression" 7 hours after the injection of 160 μg of morphine.

Thus, in contrast with subcutaneous administration, epidural injection of analgesic doses of the opiates produced no significant ventilatory effects at or after the time of analgesia, although the higher doses of fentanyl and sufentanil did depress ventilation, but relatively soon after the injection.

An earlier study (16) indicated that the μg/kg doses at which epidural opiates produce analgesia in this rat preparation (17) are predictive of the doses at which the same compounds produce analgesia upon epidural injection in humans. In view of this correlation, the conclusions from the animal experiments reported here appear consistent with observations in humans (8,26,27) that analgesic doses of opiates cause less respiratory effect after epidural than after systemic administration. Specifically, analgesic doses of epidural morphine (28–30), meperidine (31–33), fentanyl (34–37), and sufentanil (38) produce little or no respiratory effects in patients (but see 39,40), though epidural morphine in volunteers (13,14,41,42) is associated with respiratory depression.

That volunteers develop respiratory depression with analgesic doses (i.e., 2–10 mg) of epidural morphine (13,14,41,42) contrasts with the present findings that presumably (16) equivalent doses of morphine (i.e., 40 μg) and the other opiates had no significant effect in the present experiments (Fig. 2). However, control $\dot{V}_E$ immediately (i.e., 15 minutes) after epidural injection of saline (i.e., 207 ± 11 ml · min^{-1} · 100 g^{-1}) was considerably higher (two-tailed $P < .001$; Mann–Whitney U-test) (19) than the 169 (± 7.0) value which was obtained after 4 hours and the 163 (± 5.3) value in the subcutaneous control experiments. This ventilatory stimulation 15 minutes after epidural saline injection may well result from stress caused by manipulation during injection (43,44) and may have masked possible respiratory effects of the opiates soon after their injection. This suggested mechanism may also account for the above-mentioned differences in respiratory effects of epidural opiates between volunteers and patients suffering pain and is consistent with findings that opiate-treated subjects may show sudden respiratory depression upon removal of stressful (e.g., nocicep-

tive) stimulation (46,47); at that time the opiate continues to act on the respiratory center.

It is thus conceivable that, in addition to the suggested role of lipid solubility and transport through CSF (50), duration of action and dissociation rate may determine the extent to which respiratory depression occurs after the epidural injection of opiate analgesics. Research on the interactions of stressors with the respiratory effects of opiates with different dissociation half-life periods is needed to understand and control more effectively the respiratory depression that may occur late after epidural injection of opiates.

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Topical Anesthesia of the Skin by Liposome-Encapsulated Tetracaine

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GESZTES A, MEZEI M. Topical Anesthesia of the skin by liposome-encapsulated tetracaine. Anesth Analg 1988;67: 1079–81.

The potential of a liposomal local anesthetic formulation to provide topical anesthesia of the intact skin was investigated. Tetracaine base 0.5% was encapsulated into multilamellar phospholipid vesicles. The topical anesthetic effects of the liposomal and a control (Pontocaine cream) preparation were evaluated by pinprick technique in adult volunteers. Liposomal tetracaine-produced anesthesia, which lasted at least 4 hours after 1 hour application under occlusion. Pontocaine cream was ineffective. The liposomal formulation appeared to be suitable to provide long lasting anesthesia of the skin with low drug concentration.

Key Words: ANESTHETICS, LOCAL—tetracaine, liposome-encapsulated.

Liposomes—vesicles consisting of phospholipid membranes—have been studied in recent years to alter the pharmacokinetic properties of drugs encapsulated into them (1). Their potential as drug carriers in topical preparations involving corticosteroids (2), econazole, progesterone (3), and methotrexate (4) has been evaluated. Liposomal formulations delivered more of these drugs into the skin than did conventional vehicles, and also localized them at the desired site of action (5).

Safe enhancement of penetration of local anesthetics would be required to achieve anesthesia of the skin without the preceding pain of injection. An optimal formulation to overcome the stratum corneum barrier without adverse effects has been sought by many investigators (6–9). High drug concentrations and long application times were common features of all preparations tested (6–9). The most utilizable today is a cream containing 5% eutectic mixture of lidocaine and prilocaine (EMLA), which requires 1 hour application under occlusion (10,11). A recent study of the percutaneous absorption of several local anesthetic agents suggested tetracaine as perhaps the most suitable drug candidate to create an effective formulation (12). Tetracaine had the highest permeability coefficient in vitro and the best topical anesthetic effect in vivo.

In this study we conducted a volunteer trial of a formulation, which contained liposome-encapsulated tetracaine, to assess its topical anesthetic potency.

Materials and Methods

Preparation of Liposomes

Tetracaine base (pharmacopoeal grade) 0.5% was encapsulated into multilamellar phospholipid vesicles according to the method described by Mezei and Nugent (13). The lipid phase, consisting of 7% soya phosphatidylcholine (NC-95-H, American Lecithin Co., Atlanta, Georgia), 0.7% stearic acid U.S.P. (Fisher Scientific Co.), 0.7% cholesterol (Sigma Chemical Co.), and 0.5% tetracaine base, was dissolved in chloroform:methanol 2:1 v/v in a pear-shape flask, and glass beads were added. The solvent was evaporated to dryness in a rotary evaporator under reduced pressure at 34°C, until a smooth, thin lipid film was obtained on the surface of the flask and glass beads. The film was hydrated with an aqueous phase containing 0.65% $NaHCO_3$, 0.45% NaCl (BDH Chemicals), 10% ethanol, and 7% propylene glycol in distilled water, by shaking for 30 minutes in a Lab-Line Orbit Environ-Shaker at 55°C. All solvents used (Fisher Scientific Co.) were glass-distilled. The liposomes were separated from the glass beads by filtering through a Buchner funnel without using a filter

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paper. The percentages (w/w) indicate final concentration of the components in the product.

In Vivo Study

Twenty-four healthy adult volunteers (16 female, 8 male) participated in the trial after giving written informed consent. The study was approved by the Ethical Committee of the Faculty of Health Professions of Dalhousie University. Liposomal tetracaine was compared to a commercial preparation, Pontocaine cream (Tetracaine hydrochloride equivalent to 1% tetracaine base, manufactured by Winthrop Laboratories, Aurora, Ontario, lot no 120 BL). Each subject was tested with a liposomal preparation on one arm and Pontocaine cream on the other, in a random fashion. A volume of 0.2 ml of the preparations to be tested measured by a tuberculin syringe was applied to a 10-cm^2 area marked by ink on the volar surface of the forearm and covered by Blenderm tape (3M Co., St. Paul, Minnesota) to provide occlusion. The application time was 30 minutes in one group (12 subjects) and 1 hour in the other (12 subjects); the preparations were then thoroughly wiped off the test site with a tissue paper and the anesthesia was tested by the pinprick method (3). Ten pricks covering the whole test area were carried out immediately after removal of the preparations and 30 minutes, 1 hour, 2 hours, and 4 hours afterward. The number of painless scores out of the ten noted by the volunteers was used as a measure of anesthesia. Although the appearance of the preparations was not identical, the volunteers and the evaluator were not aware of the identity of the preparations.

The effectiveness of tetracaine liposomes compared to Pontocaine cream was assessed by paired *t*-tests and significance levels were calculated. Differences were considered to be significant if $P < 0.05$

Table 1. Mean Painless Scores after 30 Minutes Application of 0.5% Tetracaine Liposome Preparation and Pontocaine Cream*

Time after start of application (hours)	Liposome preparation		Pontocaine cream		
	Mean	SD	Mean	SD	*P* Value
0.5	2.75	3.25	0.25	1.73	0.0644
1.0	5.50	3.94	1.08	1.98	0.0117
1.5	6.75	3.28	1.08	1.68	<0.0001
2.5	8.25	2.45	1.08	1.31	<0.0001
4.5	8.33	2.31	0.25	0.62	<0.0001

$N = 12$.
Statistical analysis by paired *t*-tests.
*Winthrop Laboratories, Ontario, lot 120 BL

Table 2. Mean Painless Scores after 1 Hour Application of 0.5% Tetracaine Liposome Preparation and Pontocaine Cream

Time after start of application (hours)	Liposome preparation		Pontocaine cream		
	Mean	SD	Mean	SD	*P* Value
1.0	6.25	3.65	0.08	0.29	<0.0001
1.5	8.08	2.27	0.41	0.99	<0.0001
2.0	8.83	1.47	0.25	0.62	<0.0001
3.0	9.50	0.67	0.33	1.15	<0.0001
5.0	8.75	1.48	0.16	0.57	<0.0001

$N = 12$.
Statistical analysis by paired *t*-tests.

Results

Liposomal tetracaine was found to produce long lasting anesthesia of the intact skin. The degrees of anesthesia at different times during 4 hours of testing are shown in Tables 1 and 2. Anesthesia was present after application of liposomal tetracaine whether for 30 or 60 minutes. Mean painless scores indicated that the onset of reliably deep anesthesia was between 30 minutes and 1 hour. The differences between the effects of liposomal tetracaine and Pontocaine cream were statistically significant at every time point 1 hour after application. The anesthetic effect lasted until the end of the experiment. In fact, most volunteers reported that the numbness at the test sites persisted several hours longer after the testing had been completed. Pontocaine cream was found to be ineffective, in agreement with the report of Dalili and Adriani (15). Slight erythema at the site of 1 hour application of the liposomal preparation was observed in two subjects, which resolved spontaneously within 3 hours. Both subjects were retested with an "empty" (without drug) liposome preparation later, without adverse effects.

Discussion

Tetracaine was chosen as the active ingredient because it is a potent topical anesthetic, and also convenient for liposomal encapsulation owing to its relatively large hydrophobic moiety that anchors the molecule in the phospholipid bilayers. The method used for encapsulation is simple and can be scaled up. The liposome formulation tested in these experiments acquires a gel-like consistency on cooling to room temperature, which makes it suitable for topical application.

Comparison of the topical anesthetic effect of liposomal tetracaine with that of other products reported in the literature (6–11, 14) reveals that the liposomal formulation of tetracaine is highly effective. The very low drug concentration (0.5%) is a considerable advantage, as it minimizes potential toxicity. The duration of action was also remarkably long. The interindividual variation in the onset time was large, because anesthesia was present only in 30% of the subjects after 30 minutes application. The depth of anesthesia was not tested, except in one instance when the sterile needle was used to puncture the skin to estimate the depth of numbness. The needle was inadvertently inserted deep enough to induce bleeding, but no pain was felt. One of the authors underwent surgery (removal of superficial skin lesion) under the topical anesthesia provided by the preparation (1 hour application) and felt no pain during the procedure.

Certainly, the ultimate value of the liposomal tetracaine preparation can be fully assessed only in clinical trials. Such a formulation would most probably fulfill the need for a topical anesthetic preparation capable of providing anesthesia adequate for venipuncture, minor plastic surgery, taking of split skin grafts, and so on. Also, anesthesia should last several hours after the procedure to decrease discomfort. Although the onset of action is not immediate, the preparation could be dispensed to patients for self-administration well in advance of painful procedures, because its drug content does not exceed that of the nonformulary medications used to treat insect bites, minor burns, and so on.

The mechanism by which the liposomes enhance the penetration of drugs into the skin and localize them is not completely understood. Penetration of the vesicles into the skin (5) or direct transfer of the drug between the phospholipid bilayers and the lipid content of the skin (16) have been proposed.

This new drug delivery system appears to be a promising vehicle for topical drugs. Its main ingredients, phospholipids and water, are natural components of the skin, thus highly compatible, biodegradable, and nontoxic. The minor adverse reaction in the two subjects was most likely caused by tetracaine, ester type agent, and not by the liposomal vehicle.

The development of an effective and safe topical anesthetic preparation seems feasible using this approach. The effects of phospholipid composition and different additives on the release and penetration of drug remains to be studied in detail. Other local anesthetic compounds might prove to be suitable for this purpose, when encapsulated into liposomes.

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A Dose–Response Study of Intrathecal Morphine: Efficacy, Duration, Optimal Dose, and Side Effects

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JACOBSON L, CHABAL C, BRODY MC. A dose–response study of intrathecal morphine: efficacy, duration, optimal dose, and side effects. Anesth Analg 1988;67: 1082–8.

We performed a double-blind study of the dose–response relationship of intrathecal morphine (0, 0.3, 1, and 2.5 mg) for postoperative pain relief in 33 subjects who underwent total knee or hip replacement surgery. Assessments commenced 1 hour after the opioid injection, which was given at the end of surgery, and continued for 24 hours. Pain measurements, supplementary analgesia requirements, and adverse effects were recorded. Intrathecal morphine provided effective, long-lasting pain relief. All doses delayed the initial perception of discomfort (T-Pain) and also postponed the onset of severe pain requiring analgetic supplementation (T-Morphine) (1.25 hours control with placebo injections; > 20 hours with intrathecal morphine 0.3, 1, and 2.5 mg: $P < 0.05$). Although 0.3 mg usually provided good analgesia it was unsatisfactory in three of 10 patients (30%), whereas 1 and 2.5 mg were absolutely reliable. Respiratory depression (increased $Paco_2$), common after the administration of 1 or 2.5 mg intrathecal morphine, was slow in onset and prolonged. The respiratory depression after 2.5 mg was more profound than after 1 mg, and produced apnea necessitating large-dose naloxone therapy. Pruritus was unique to intrathecal morphine administration, but nausea, vomiting, and urinary retention were common in all the groups. We conclude that no ideal dose of intrathecal morphine exists because, even with small quantities, minor adverse effects are evident. Doses between 0.3 and 1 mg, however, should provide good analgesia free from the major complication, respiratory depression.

Key Words: ANALGESICS, MORPHINE—intrathecal. ANESTHETIC TECHNIQUES, SPINAL—morphine. PAIN—postoperative.

Intrathecal morphine is an effective, convenient, and simple method for management of postoperative pain. A single dose often suffices as the sole parenteral analgesic in the postoperative period after major orthopedic procedures on the hip (1). Provided rostral spread within the cerebrospinal fluid (CSF) is curtailed, small doses of opioid confined to the neuraxis cause minimal central depression or other systemic opioid side effects (2). This is particularly advantageous in elderly and frail patients in whom systemic opioid side effects, inadequate analgesia, and adverse hormonal and metabolic responses to surgery and anesthesia may interact with pre-existing systemic illnesses to increase morbidity and mortality (3,4).

There is little systematically documented information about the analgetic properties, optimum dose, and adverse effects of intrathecal morphine, particularly in elderly patients. Therefore, it is difficult to formulate rational treatment guidelines for the routine use of this method of handling postoperative pain. Consequently, we studied a range of doses and compared the analgetic and adverse side effects with findings in a control group of subjects who received no intrathecal opioid.

Methods

The project was approved by our human subjects review board and written informed consent was obtained from each patient before the operation. Subjects for the study were 33 men scheduled for total knee or hip replacement. Relevant patient data are outlined in Table 1.

The subjects were divided into four groups: 1) 0 mg morphine ($n = 10$); 2) 0.3 mg morphine ($n = 10$); 3) 1 mg morphine ($n = 10$); and 4) 2.5 mg morphine ($n = 3$). After prolonged apnea occurred in three pa-

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Table 1. Clinical Data*

	Intrathecal morphine dose (mg)			
	0	0.3	1	2.5
n	10	10	10	3
Age (years)	65.5 ± 3.3 (60–73)	63.5 ± 5.3 (53–74)	63.5 ± 5.0 (51–72)	64 (53–66)
Weight (kg)	81.5 ± 10.5 (68–128)	87 ± 16 (61–109)	94 ± 9 (75–113)	96 (76–112)
Height (cm)	174 ± 5 (155–190)	176.5 ± 3.5 (168–190)	179 ± 6.5 (155–189)	183 (165–183)

*Data are median ± quartile deviation with ranges in parentheses.

tients, their sealed study envelopes were opened. It was discovered that all had received 2.5 mg of morphine and consequently this dose was discontinued. The patients were randomly assigned to a treatment group and the drug was administered in a double-blind manner. Commercially available preservative-free morphine (Duramorph), 1 mg/ml, was used, and all injectates were standardized to a volume of 2.5 ml with sterile water, if needed. The opioid was injected intrathecally at the end of the surgical procedure. The control subjects (0 mg morphine) received 2.5 ml of sterile water intrathecally.

No premedication was given and systemic opioids were withheld until requested or deemed necessary in the postoperative period, when small incremental doses of intravenous morphine were given until satisfactory analgesia (nil or mild discomfort) was obtained. Subsequently morphine was administered intramuscularly according to the patients' requirements. The time at which initial discomfort (T-Pain) occurred was recorded, as were the times when supplementary morphine analgesia was given (T-Morphine).

Assessments conducted by an investigator unaware of the constituents of the subarachnoid injection started one hour after the injection of morphine and continued for a minimum of 24 hours or longer until the effects of the morphine had receded. The observations were conducted at hourly intervals for the first 6 hours, then every 2 hours for the next 6 hours, and finally at 4-hour intervals. All patients were kept in the postanesthesia recovery unit (PARU) and/or the surgical intensive care unit (SICU) overnight.

Patients assessed pain and analgetic effect of intrathecal morphine by means of a modified rank pain scale (RPS) (5) and a numerical pain rating system (6,7). In the latter, patients gave a verbal number from 0 to 10: 0 representing no pain and 10 the worst pain imaginable. The RPS corresponded to nil, mild, moderate, severe, or unbearable discomfort.

Dermatomal levels of altered neural function after intrathecal injections of morphine were evaluated by testing somatic motor function and blunt pinprick as well as cold (ethyl chloride spray) discrimination. Heart rate and blood pressure were recorded. Adverse effects monitored included pruritus, nausea, vomiting, excessive sedation, urinary retention and reduction in respiratory frequency (*f*). Respiratory frequency was measured with the subjects at rest and undisturbed, and prior to making the remaining observations. Repeated measurements of arterial blood gas tensions were made, under the same undisturbed circumstances, in 28 patients who had indwelling arterial cannulae.

Statistical analysis of differences in times to the onset of discomfort, times until supplementary morphine was needed, and the numerical pain scores were accomplished using the Kruskal–Wallis analysis of variance by ranks (8). Qualitative data were analyzed by the Fisher exact probability test. A probability of less than 0.05 ($P < 0.05$) was considered statistically significant.

Results

There were no significant differences between the four groups in age, weight, or height (Table 1). The median time to the initial perception of discomfort (T-Pain) for the 0, 0.3, 1, and 2.5 mg groups was 1, 11.5, 13, and 38 hours, respectively (Table 2). In all three opiate groups complete absence of discomfort lasted significantly longer than in the control group (0 mg). Three of five patients given intrathecal morphine who complained of discomfort at 1 hour, were pain-free at 2 hours.

In patients given intrathecal morphine the time to onset of discomfort severe enough to require supplemental morphine was also longer than it was in patients given no intrathecal morphine ($P < 0.05$) (Table 3). The median time to initial supplementary analgesia was markedly increased after intrathecal morphine, being 1.25, 21.25, 29, and 38 hours for the 0, 0.3, 1, and 2.5-mg groups, respectively. Although 0.3 mg usually provided satisfactory and prolonged analgesia, it did not postpone the need for morphine supplementation in three patients (30%) who re-

Table 2. Time in Hours to Onset of Discomfort after Intrathecal Injection in the Four Groups of Patients

	Intrathecal morphine dose (mg)			
	0	0.3	1	2.5
Median	1	11.5	13	38
Interquartile range	0	1.5–23	2–27	—(1–50)*

*Insufficient data (n = 3). Range in parentheses.

Table 3. Time in Hours between Initial Intrathecal Injection and the Need for Supplemental Analgesics

	Intrathecal morphine dose (mg)			
	0	0.3	1	2.5
Median	1.25	21.25	29	38
Interquartile range	0	4–28	26–31	—(26–50)*

*Insufficient data (n = 3). Range in parentheses.

Table 4. Median Pain Score on a Verbal Scale of 0 to 10

Time in hours after intrathecal injection	Intrathecal morphine dose (mg)			
	0	0.3	1	2.5
1	5	0	0	3
2	6	0	0	0
3	5	0	0	0
4	3	0	0	0
5	3	1	0	0
6	5	0	1	0
8	5	0	0	0
10	5.5	0	0.5	0
12	5	0	0	0
16	3.5	0	0	0
20	3	2	1	0

Table 5. Amounts of Supplemental Systemically Administered Morphine in the First 24 Hours

	Intrathecal morphine dose (mg)			
	0	0.3	1	2.5
Median	45	5	0	0
Interquartile range	20–85	0–20	0–5	—(0)*

*Insufficient data (n = 3). Range in parentheses.

quired additional analgesia 2.5, 3, and 5 hours after the intrathecal injection.

Analysis of the pain scores at the various time intervals showed a significant difference between the treatment and control (0 mg) groups (Table 4). The frequency of occurrence of satisfactory analgesia (mild or no discomfort) was significantly greater in patients given morphine intrathecally.

The total amounts of supplementary morphine needed, and the number of doses of additional morphine required in the 24 hours after the subarachnoid injection, were significantly less in the morphine categories than in the control group (Tables 5 and 6). Patients given the higher doses (i.e., 1 and 2.5 mg) required less supplementation than those given 0.3 mg.

Respiratory depression (diminished respiratory rate and elevated $Paco_2$) was common after 1 or 2.5 mg intrathecal morphine (Table 7). The latter dose caused severe ventilatory inhibition (apnea) requiring high dose naloxone therapy in three consecutive cases; consequently, this dose was discontinued. Each of these three patients described the gradual onset of drowsiness 2–3 hours after the intrathecal

Table 6. Number of Supplemental Systemically Administered Morphine Doses in the First 24 Hours

	Intrathecal morphine dose (mg)			
	0	0.3	1	2.5
Median	6	0.5	0	0
Interquartile range	3.5–10	0–4	0–0.5	—(0)*

*Insufficient data (n = 3). Range in parentheses.

Table 7. Adverse Effects

	Intrathecal morphine dose (mg)			
	0	0.3	1	2.5
Pruritus	0/10	9/10	10/10	1/3
Nausea/vomiting	6/10	5/10	10/10	2/3
$f < 10$ breaths/min	0/10	1/10	6/10	3/3*
$Paco_2 > 50$ mm Hg	0/8	1/8	6/9	0/3*
Urinary retention requiring catheterization	5/9	5/6	7/7	2/2

*These subjects were stimulated by verbal arousal and naloxone infusion.

Table 8. Effect of Intrathecal Morphine on $Paco_2$

	Intrathecal morphine dose mg*		
Time in hours after intrathecal injection	0	0.3	1
0	39.5 ± 3 (37–45)	40.5 ± 2.5 (37–44)	38 ± 3.3 (35–44)
1	39.5 ± 2 (33–42)	41 ± 2 (38–47)	38 ± 5.3 (34–47)
2	38 ± 2 (27–41)	40 ± 2 (36–45)	42 ± 3 (38–59)
3	38 ± 2.5 (31–44)	40 ± 1 (38–44)	42 ± 2.6 (39–57)
4	38.5 ± 1 (34–46)	37 ± 2.5 (33–47)	44 ± 4.4 (35–55)
5	40 ± 3 (34–45)	38 ± 4 (32–46)	48 ± 3.9 (41–58)
6	39 ± 1 (36–46)	39.5 ± 3 (35–47)	45 ± 6.4 (37–61)
8	39 ± 2.5 (36–42)	38.5 ± 3 (34–42)	45 ± 6.9 (38–54)
10	39 ± 2 (35–42)	37.5 ± 3 (33–50)	47 ± 7.1 (36–58)
12	37 ± 0.5 (36–40)	38.5 ± 2.5 (32–46)	45 ± 5.8 (38–55)
16	38.5 ± 1 (35–42)	36.5 ± 3 (30–44)	43 ± 6.1 (38–52)
20	36.5 ± 3 (33–43)	38.5 ± 2 (34–42)	40 ± 3.1 (34–49)

*Data are in mm Hg and expressed as median ± quartile deviation with ranges in parentheses.

injection, and became apneic within 1 hour thereafter. Their condition was characterized by an overwhelming desire to sleep if left undisturbed. However, these three patients were all easily rousable and maintained satisfactory spontaneous ventilation if kept awake. Large quantities of naloxone (10, 11, and 13 mg) administered in incremental bolus doses combined with a constant infusion of naloxone were required for 16–22 hours. The naloxone infusion rate was adjusted according to the subject's ability to breathe spontaneously and to remain awake. The combination of verbal arousal and naloxone infusion maintained satisfactory ventilation. Effective postoperative analgesia was maintained throughout the naloxone infusion period.

One milligram of intrathecal morphine also produced ventilatory depression heralded by the gradual onset of drowsiness and the elevation of the $Paco_2$ at 2–4 hours. Peak respiratory depression occurred between 5–10 hours and then slowly decreased to baseline levels by 20 hours (Table 8). All the patients given 1 mg morphine maintained spontaneous ventilation without naloxone administration, and remained easily rousable throughout the duration of the study. The median $Paco_2$ levels with 1 mg were consistently significantly higher than with 0 or 0.3 mg during the 4–16 hour observation period (Table 8). In the latter groups (0, 0.3 mg) the median $Paco_2$ remained within normal limits.

After 1 mg intrathecal morphine, f usually decreased as $Paco_2$ increased, so that between 2 and 16 hours f was consistently lower than with 0 and 0.3 mg, when f remained constant (Table 9). The median f reflected this change. A decrease in f was not seen in all patients and a few subjects had increases in $Paco_2$ with f values above 10 breaths/min.

Table 9. Effect of Intrathecal Morphine on Respiratory Rate

Time in hours after intrathecal injection	Intrathecal morphine dose (mg)*		
	0	0.3	1
0	19 ± 2.5 (12–26)	17 ± 3 (12–24)	17 ± 2 (14–20)
1	18 ± 4 (12–22)	18 ± 2.8 (12–24)	16 ± 2.5 (12–20)
2	16 ± 1.5 (12–20)	15.5 ± 2.5 (9–20)	12 ± 3.3 (10–18)
3	18 ± 2.5 (12–20)	15.5 ± 3 (11–24)	13.5 ± 3 (6–18)
4	17 ± 2.25 (12–20)	15.5 ± 2.8 (12–22)	11 ± 1.8 (8–20)
5	16 ± 1.5 (12–20)	16.5 ± 3 (14–22)	11.5 ± 4 (6–20)
6	16 ± 1.75 (14–18)	16 ± 3 (14–20)	11 ± 2 (7–16)
8	17 ± 2.5 (14–20)	16 ± 3.3 (11–22)	12 ± 4.5 (8–18)
10	16 ± 1.5 (12–18)	16 ± 2.3 (10–20)	12 ± 2.8 (7–18)
12	17 ± 2 (12–20)	18 ± 1.3 (14–22)	13 ± 3 (7–19)
16	16 ± 2 (12–20)	16 ± 2 (14–20)	12 ± 2.3 (10–18)
20	16 ± 1.5 (14–18)	16 ± 2 (14–24)	15 ± 1.5 (12–20)

*Data are in breaths/min and expressed as median ± quartile deviation with ranges in parentheses.

The potency of intrathecal morphine was illustrated by the three within patient comparisons (double-blinded, crossover) that were conducted on subjects who underwent two sequential operations for bilateral hip and/or knee degenerative disease. Two subjects received 0 mg followed by 1 mg or vice versa. After 0 mg, discomfort requiring supplementary morphine occurred shortly after the intrathecal injection (2.5 and 1.25 hours) and large quantities of morphine were required in the first 24 hours after the operation (32 and 45 mg). No respiratory depression was evident. When the same subjects received 1 mg they had excellent and long lasting analgesia (23 and 29 hours) requiring only 10 mg (1 dose) and 0 mg morphine supplementation, respectively, in the first 24 hours after the operation. Both had appreciable ventilatory depression. The third patient received 0.3 mg both times and had excellent analgesia without respiratory effects on both occasions.

Pruritus was frequently encountered ($P < 0.05$) in the patients given intrathecal morphine, and was absent in the control (0 mg) group (Table 7). The nose, face, trunk, and perineum were most frequently involved. Itching was gradual in onset, usually first noticeable 2 hours after the injection and lasting from 2–24 hours, with larger doses (1 mg) producing more prolonged itching. Pruritus was usually minor and required no treatment.

Urinary retention was frequent in all groups and no significant difference was apparent in the incidence of catheterization of the bladder (Table 7). However, among the patients given intrathecal morphine, only one (in the 0.3 mg group) managed to void spontaneously. Nausea and vomiting were frequent and similar in frequency in all groups including the controls (0 mg) (Table 7).

All patients were easily rousable. The majority had some drowsiness associated with a pleasantly relaxed and serene sensation. Patients given 2.5 mg, on the other hand, had an overwhelming urge to sleep that was associated with apnea. However, a gentle tap on their shoulder and/or a quiet word in their ear restored consciousness and spontaneous ventilation. No clinical evidence of circulatory depression, motor, or sensory impairment was identified.

Discussion

The ability of morphine to provide analgesia when injected into the subarachnoid space has been well-demonstrated (9–11). However, the dose of intrathecal morphine that provides the best analgesia with the fewest side effects has not been defined. There are no reliable dose–response data for a broad range of intrathecal morphine doses, and those that are available have been gleaned from a retrospective survey (12). For example, a wide range of doses, 0.1 mg to 20 mg, have been reported as providing excellent analgesia, devoid of adverse effects (13,14). However, studies using low dose intrathecal morphine have also found that 0.2 mg was not as effective as 0.4 mg in preventing postoperative pain (15), thereby placing the reliability of low dose intrathecal morphine in doubt. Furthermore significant respiratory depression has occurred with only 0.8–1 mg intrathecal morphine (16,17).

Various factors have complicated the interpretation of the results of published studies of intrathecal morphine for the relief of postoperative pain. Its injection at induction of anesthesia makes evaluation of the early phases of intrathecal opioid effects impossible. Intrathecal morphine has been mixed with local anesthetic, dextrose, epinephrine, and/or saline, which may augment, inhibit, and/or obscure the effects of morphine itself (9,14,18–22). Perioperative

administration of supplementary opioids and long-acting sedatives (12,15,18) may act synergistically with the intrathecal morphine. Because of prolonged sedation and altered cognition, such drugs may also prevent the accurate assessment of postoperative analgesia.

In this study, we attempted to circumvent these problems by injecting the intrathecal morphine at the end of surgery, thereby avoiding its mixture with local anesthetics, dextrose, or epinephrine. Observations on the early effects of intrathecal morphine could also be made free of intraoperative considerations. The perioperative administration of supplementary opioids and long acting sedatives was also avoided. To avoid possible neural responses to saline (20), sterile water was used as the diluent. The double-blind nature of the study was ensured by using a constant volume of injectate (2.5 ml) determined by the 2.5 mg dose (Duramorph, 1 mg/ml). The placebo control group received only 2.5 ml water intrathecally. The use of water as the diluent for the morphine posed a theoretical problem of the ensuing hypobaric solution migrating rostrally to produce respiratory depression. However, 2.5 mg morphine with no water added reliably produced apnea while 0.3 mg (2.2 ml water added) and 1 mg (1.5 ml water added) did not.

Observations began 1 hour after the operation to permit levels of residual operative anesthesia to recede. Although we were unable to measure onset of action, some subjects given either 1 mg or 2.5 mg morphine had pain at the initial 1 hour assessment but were pain-free 2 hours after injection. Furthermore, the lowest pain scores were consistently observed at or beyond 2 hours. The morphine presumably required this period of time to bind to the CNS opioid receptors in sufficient quantities to produce satisfactory pain relief.

It was difficult to apply the standards proposed for the assessment of pain (23) to elderly patients who had major surgery, because in the early postoperative period their ability to cooperate is limited. Consequently we used verbal pain ratings in the form of a modified rank pain chart (5) and a verbal adaptation of the 11-point box scale (BS-11), a 0 to 10 rating system to ascertain the quality of analgesia (6,7). The latter is used routinely in our chronic pain service and allows a reliable assessment of discomfort by the patient. In the early postoperative period, a verbal pain score was more reliable, in our hands, than the traditional written one (23).

The quality of analgesia provided by intrathecal morphine was excellent, but side effects were common. This confirms other studies, which found that epidural morphine produced more profound analgesia than either intravenous, patient-controlled morphine analgesia or intramuscular therapy (24,25). However, intrathecal morphine was associated with bothersome side effects and the risk of respiratory depression.

There was a dose–response relationship for analgesia with intrathecal morphine. Three tenths of a milligram produced analgesia that, although better than no morphine (0 mg), was on occasion erratic and generally of shorter duration than that produced by 1 mg or 2.5 mg. Our observations on the relative unreliability of 0.3 mg are corroborated by others who found that small doses of intrathecal morphine (0.2 mg) (15) were not as effective as larger doses in providing prolonged postoperative analgesia. It was difficult in our study to evaluate differences between 1 mg and 2.5 mg, because of the small number of subjects given the latter dose. However, in patients undergoing major orthopedic surgery, a ceiling effect was reported on the time to first analgesia with intrathecal morphine doses of 1.25 mg or greater (12).

The delayed onset and sustained respiratory depressant effect with 1 mg and 2.5 mg morphine probably reflected lingering amounts of relatively insoluble morphine in the CSF that migrated rostrally within the CSF to the vicinity of the brain-stem respiratory areas (26) and finally penetrated slowly to these vital centers. The occurrence of respiratory depression was dose related with 0.3 mg producing little respiratory effect, 1 mg producing significant inhibition but still with maintenance of spontaneous ventilation, whereas 2.5 mg precipitated apnea. The elevations in $Paco_2$ were late in onset and sustained. This pattern of ventilatory inhibition was explicable in terms of the behavior of morphine when deposited in large quantities within the lumbar CSF (27–29). Large doses of naloxone were required to maintain spontaneous ventilation after 2.5 mg intrathecal morphine (30), the initial doses of naloxone being at the upper limit recommended for the treatment of an acute narcotic overdose. The initial infusion rates of naloxone required to maintain spontaneous breathing were also greater than those recommended for the prevention of side effects from intrathecal morphine (31). Analgesia remained satisfactory, however, despite the large amounts of naloxone required (32) to ensure adequate ventilation.

Intrathecal morphine provided excellent analgesia. Low doses (0.3 mg) were associated with an inconsistent duration of analgesia and undesirable side effects. Larger doses (1 mg and 2.5 mg) provided reliable and prolonged analgesia, but were often accompanied by respiratory depression. Thus, there

is no ideal dose of intrathecal morphine for the relief of postoperative pain, because even with low doses, minor adverse effects are evident. The best dose appears to lie between 0.3 mg and 1 mg; it will predictably provide superior analgesia free from adverse ventilatory effects, even though associated with undesirable non-ventilatory side effects.

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Combined H_1 and H_2 Receptor Blockade Attenuates the Cardiovascular Effects of High-Dose Atracurium for Rapid Sequence Endotracheal Intubation

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HOSKING MP, LENNON RL, GRONERT GA. Combined H_1 and H_2 receptor blockade attenuates the cardiovascular effects of high-dose atracurium for rapid sequence endotracheal intubation. Anesth Analg 1988;67:1089–92.

Large doses of atracurium (1.5 mg/kg) (six times the ED_{95}) can result in significant histamine release, resulting in systemic hypotension. The efficacy of histamine receptor blockade in attenuating atracurium induced hypotension was therefore studied. Four groups of seven patients each were studied: group I, control; group II, H_1 blockade (1 mg/kg diphenhydramine); group III, H_2 blockade (cimetidine 4 mg/kg); and group IV, H_1 and H_2 blockade (diphenhydramine 1 mg/kg and cimetidine 4 mg/kg). All patients were anesthetized with an intravenous narcotic–nitrous oxide technique and then given 1.5 mg/kg atracurium.

In group I, mean arterial pressure (MAP) decreased 30 mm Hg after 2 minutes and remained 25 mm Hg below baseline at 3 minutes, a change significantly greater than that in group IV, in which MAP decreased 8 and 7 mm Hg, respectively. H_1 receptor blockade was associated with no significant attenuation of changes in MAP. H_2 receptor blockade alone was associated with significant decreases in MAP, possibly secondary to enhanced release of histamine via an antagonist effect on recently described H_3 receptors. Plasma histamine levels increased significantly 2 minutes after atracurium administration and correlated with hemodynamic changes. It is concluded that combined H_1 and H_2 receptor blockade attenuates cardiovascular effects associated with large doses of atracurium in humans. Histamine-releasing agents may be contraindicated in patients subject to chronic H_2 receptor blockade.

Key Words: NEUROMUSCULAR RELAXANTS—atracurium. HISTAMINE—antagonists.

Succinylcholine is the current agent of choice for clinical situations requiring rapid induction of anesthesia and tracheal intubation. However, certain conditions or diseases contraindicate the use of succinylcholine, including burns (1), massive tissue trauma (2), intra-abdominal infection (3), increased intraocular pressure (4), and a host of neuromuscular diseases that alter neuromuscular function (5,6). For these patients, an alternative means of providing adequate muscle relaxation for rapid sequence tracheal intubation is important.

Lennon et al. (7) reported adequate intubating conditions within 60 seconds when using doses of atracurium (1.5 mg/kg) or vecuronium (0.25 mg/kg), about six times the ED_{95}. While vecuronium was without apparent hemodynamic side effects virtually regardless of dose, at this high dose atracurium caused hypotension and tachycardia, presumably secondary to histamine release. Therefore, use of histamine blockers might improve the utility of atracurium by preventing these side effects. Scott et al. (8) demonstrated the efficacy of combined histamine-receptor blockade in attenuating the cardiovascular effects of 0.6 mg/kg IV atracurium. However, the same authors reported incomplete moderation by histamine-receptor blockade of hemodynamic effects when using atracurium 0.8 mg/kg IV bolus for rapid induction (9). While high dose vecuronium causes little or no hypotension and tachycardia, prolonged recovery from paralysis in patients with even mild hepatic dysfunction has been reported (10). If the cardiovascular effects of high dose atracurium could be attenuated by histamine antagonists, it would provide an excellent alternative for clinical situations in which succinylcholine is contraindicated.

Pilot studies in rabbits in our laboratory indicated that combined histamine-receptor blockade pre-

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vented the hemodynamic changes that occur with high dose atracurium administration. In this context, we sought to extend our preliminary observations concerning high dose atracurium in humans, and to determine if histamine blockade would effectively prevent hypotension.

Methods

Four groups of seven patients, ASA physical status I or II adults, were studied: a control group, an H_1-blocked group (1 mg/kg diphenhydramine), an H_2-blocked group (4 mg/kg cimetidine), and a combined H_1- and H_2-blocked group (diphenhydramine 1 mg/kg plus cimetidine 4 mg/kg). The study was approved by the Mayo Institutional Review Board and written informed consent was obtained from all patients. Patients being chronically treated with H_1 or H_2 receptor blockers, β-blockers or tricyclic antidepressants were excluded. All patients were monitored by lead V_5 of the ECG, a pulse oximeter, and a blood pressure cuff. An intra-arterial cannula was inserted in the radial artery and connected to a Gould transducer that was zeroed at midcardiac level. Arterial pressure was recorded continuously with a Gould Brush 2400 multichannel polygraph.

Anesthesia was induced with thiopental 4 mg/kg and fentanyl 3 μg/kg and maintained with 70% nitrous oxide and 30% oxygen with incremental doses of fentanyl to prevent movement. Ventilation was monitored by a Perkin-Elmer 1100 mass spectrometer and serial arterial blood gas analysis. Tidal volume, respiratory rate, and inspired gas mixture were adjusted to maintain arterial Po_2 120–150 mm Hg and Pco_2 35–40 mm Hg. Temperature was monitored with an esophageal probe; normothermia (37 ± 0.5°C) was maintained with humidification of respiratory gases and adjustment of ambient room temperature. All blood samples were replaced threefold with Ringer's lactate solution immediately after sampling.

Arterial samples for measurement of histamine levels were drawn immediately before atracurium administration (see below) and 2 and 5 minutes later. Histamine levels were determined by a double isotope enzymatic assay technique (11). Blood specimens for histamine levels were collected into chilled polypropylene tubes containing 20 μl 0.5 ethylene diamine tetraacetate, pH 7.0. These were centrifuged immediately at 4°C (15 minutes at 2000 *g*). Plasma was aspirated into polypropylene tubes and stored at −70°C until assay. Stimulating electrodes were placed over the ulnar nerve at the wrist and a Grass S88 stimulator was used to deliver a supramaximal 0.2-ms-square wave pulse at 1.0 Hz. Thumb adductor force was quantitated by a Grass FT-10 transducer and was recorded by polygraph.

All patients were pretreated with the appropriate histamine receptor blockers 30 minutes before administration of atracurium. After the patients were fully instrumented and anesthetized, an equilibration period of 10 minutes was utilized. Thiopental has been reported to cause histamine release in some instances (12), and the 10-minute equilibration period was instituted to allow elimination of any histamine possibly released during induction ($t_{\frac{1}{2}} = 2$ minutes). After the equilibration period, control heart rate and arterial pressure were recorded, and a blood specimen for baseline histamine level was drawn. The atracurium bolus dose, 1.5 mg/kg, was injected by rapid IV bolus over 3 seconds via a three-way stopcock at the cannula hub. Arterial pressure and heart rate were continuously recorded for 10 minutes and arterial samples for measurement of histamine levels were drawn 2 and 5 minutes after atracurium injection. Ten minutes after atracurium administration and completion of all data collection, the patients were intubated and mechanically ventilated.

Results are expressed as mean ± SEM. Intragroup hemodynamic data were analyzed for significance by ANOVA. Intergroup comparisons utilized an unpaired *t*-test. Statistical significance was assumed with $P < 0.05$.

Results

The results are summarized in Tables 1 and 2. Cardiovascular effects were transient, tending to peak at 2 minutes and returning to control values within 10 minutes.

Combined H_1 and H_2 blockade significantly attenuated hypotension after atracurium. This pattern differed significantly from that of the control group, in which atracurium 1.5 mg/kg IV bolus decreased MAP 30 mm Hg at 2 minutes and remained 25 mm Hg below baseline at 3 minutes after injection (Table 1). In the combined blockade group, MAP had decreased 8 mm Hg at 2 minutes ($P < 0.05$) and 7 mm Hg at 3 minutes ($P < 0.05$). H_1 receptor blockade alone resulted in no statistically significant attenuation of changes in MAP (Table 1). H_2 receptor blockade alone was associated with such profound decreases in MAP in the first three patients that no further patients in this group were studied. Heart rate did not change significantly after administration of atracurium in any of the groups.

Table 1. Response of Mean Arterial Pressure (MAP) and Heart Rate (HR) to Atracurium 1.5 mg/kg IV Bolus

Group	Baseline	1 min	2 min	3 min	5 min	7 min	10 min
Control							
MAP (mm Hg)	80 ± 5	64 ± 6	50 ± 6	55 ± 6	65 ± 9	74 ± 10	78 ± 10
HR (n = 7)	65 ± 2	75 ± 4	82 ± 5	80 ± 4	81 ± 7	79 ± 8	78 ± 9
H_1 blockade							
MAP (mm Hg)	74 ± 6	61 ± 4	61 ± 5	65 ± 5	73 ± 5	76 ± 5	77 ± 4
HR (n = 7)	69 ± 4	76 ± 5	76 ± 4	77 ± 4	75 ± 4	75 ± 5	75 ± 6
H_2 blockade							
MAP (mm Hg)	70 ± 5	55 ± 10	35 ± 5	50 ± 2	58 ± 3	67 ± 8	75 ± 11
HR (n = 3)	56 ± 4	62 ± 4	68 ± 5	64 ± 3	63 ± 3	61 ± 4	60 ± 5
Combined blockade							
MAP (mm Hg)	82 ± 4	78 ± 5	*74 ± 7	*75 ± 6	78 ± 5	80 ± 5	81 ± 5
HR (n = 7)	64 ± 3	68 ± 3	71 ± 3	71 ± 4	68 ± 4	68 ± 3	67 ± 3

*$P < 0.05$ with respect to control group at the same time interval.
Values reported are mean ± SE.

Table 2. Effect of Atracurium 1.5 mg/kg on Plasma Histamine Concentations

		Plasma histamine (pg/ml)		
Group	N	Control	2 min	5 min
Control	7	349 ± 53	6824 ± 1904*	2290 ± 567*
H_1 blockade	7	381 ± 53	8594 ± 3224*	2330 ± 781*
H_2 blockade	3	410 ± 74	10466 ± 2349*	3803 ± 1277
Combined blockade	7	621 ± 216	11010 ± 5612	2821 ± 1077

*$P < 0.05$ compared to control.

Histamine levels were increased significantly at 2 minutes and decreased towards baseline at 5 minutes (Table 2).

Discussion

We found that combined H_1 and H_2 receptor blockade attenuates the hypotensive effect of high dose atracurium 1.5 mg/kg. Within the usual clinical dose range, atracurium causes only minor histamine release and does not alter cardiovascular stability (13). However, doses above 0.5 mg/kg may cause significant hypotension and tachycardia secondary to histamine release (7,14–16). The inability of histamine receptor blockade to attenuate the hemodynamic consequences of 0.8 mg/kg IV atracurium reported by Scott et al. (9) may have been due to the timing of the pretreatment with histamine receptor blockers. Scott et al. (8) administered histamine receptor blockers 15 minutes before the atracurium bolus. Pilot studies at our institution in rabbits indicate that 30 minutes is required after pretreatment with diphenhydramine to effectively attenuate the hemodynamic consequences of high dose atracurium. Brimblecomber et al. (17) demonstrated that different antagonists vary in the rates at which they attain equilibrium with tissue, more potent antagonists generally requiring more time. Scott et al. (8) used chlorpheniramine to produce H_1 receptor blockade. Measurement of antagonist activity in guinea pig ileum strips (pA_2) indicates chlorpheniramine is a more potent H_1 antagonist than is diphenhydramine. Chlorpheniramine may, however, require more time to reach peak antagonist effect than the 15-minute period utilized by Scott et al. This may in part account for their inability to fully attenuate the hemodynamic consequences of atracurium 0.8 mg/kg IV.

Patients pretreated with the H_2 receptor antagonist cimetidine in our study developed profound decreases in MAP after administration of atracurium. This resulted in termination of the study in that group after three patients. A new class of histamine receptors (H_3) that function as autoreceptors to inhibit the synthesis and release of histamine has been recently described (18). Several H_2 receptor antagonists, including cimetidine, have been reported to exert a partial antagonist effect on H_3 receptors (19). This could lead to enhanced release of histamine and the more profound hemodynamic changes that we observed in the H_2 blockade group. H_1 receptor blockers exert negligible effects on the H_3 receptor (19). Thus H_1 receptor blockade may partially attenuate the hemodynamic consequences of histamine release and it has the advantage that it does so without potentiating histamine release.

Histamine plasma values consistently correlated with changes in blood pressure at 2 minutes and returned toward baseline levels by 5 minutes after injection of atracurium. We used a recently described double isotype assay technique (11) with enhanced sensitivity and specificity. Individual histamine response to 1.5 mg/kg atracurium IV varied widely

between individuals. Similar wide variability of histamine response to muscle relaxants has been noted in previous reports (9,20).

Changes in blood pressure correlated well with plasma histamine levels. We conclude that combined H_1 and H_2 receptor blockade effectively attenuates the cardiovascular effects secondary to release of histamine associated with high dose atracurium. Isolated blockade of H_1 and H_2 receptors was not as effective as combined blockade. H_2 receptor blockade alone resulted in profound decreases in MAP, possibly secondary to a partial antagonist effect on recently described H_3 receptors.

In conclusion, we do not recommend high dose atracurium for rapid sequence induction in patients on chronic H_2 receptor antagonist therapy, but with IV administration of combined H_1 and H_2 receptor blockade 30 minutes prior to induction of anesthesia, high dose atracurium for rapid sequence intubation provides the anesthesiologist with muscle relaxation unaccompanied by hypotension.

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Flammability of Esophageal Stethoscopes, Nasogastric Tubes, Feeding Tubes, and Nasopharyngeal Airways in Oxygen- and Nitrous Oxide-Enriched Atmospheres

Joseph I. Simpson, MD, and Gerald L. Wolf, MD

SIMPSON JL, WOLF GL. Flammability of esophageal stethoscopes, nasogastric tubes, feeding tubes, and nasopharyngeal airways in oxygen- and nitrous oxide-enriched atmospheres. Anesth Analg 1988;67: 1093–5.

This study determines the flammability of materials in the oral cavity and pharynx during anesthesia in an environment of potentially high oxygen (O_2) and nitrous oxide (N_2O) concentrations where an ignition source (cautery, laser) may be in close proximity. The materials tested included esophageal stethoscopes, Salem sump nasogastric tubes, enteric feeding tubes, and plastic and rubber nasopharyngeal airways. Flammability was determined using oxidant $_{O_2}$ and oxidant $_{N_2O}$ indices of flammability. The oxidant $_{O_2}$ and oxidant $_{N_2O}$ indices of flammability are defined as the minimum fraction of oxidant (O_2 or N_2O) in nitrogen diluent that supports a candle-like flame for a given fuel source. The oxidant $_{O_2}$ index of flammability for esophageal stethoscopes is 0.218, for Salem sump nasogastric tubes 0.229, for enteric feeding tubes 0.192, for plastic nasopharyngeal airways 0.196, and for rubber nasopharyngeal airways 0.172. The oxidant $_{N_2O}$ index of flammability for esophageal stethoscopes is 0.430, for Salem sump nasogastric tubes 0.430, for enteric feeding tubes 0.375, for plastic nasopharyngeal airways 0.415, and for rubber nasopharyngeal airways 0.366. These indices are linearly additive.

Key Words: ELECTRICAL SYSTEMS—fires. EXPLOSIONS—flammability. EQUIPMENT—flammability.

Operating room fires present a danger to both patient and personnel. Three components are necessary to produce such fires: a fuel or material to be burned, an ignition source, and an oxidizing environment. Operating room fires reported in the recent literature are of endotracheal tubes (ETTs) ignited by carbon dioxide (CO_2) lasers (1–3) and electrocautery (4). There are several reports of combustion of fuels other than ETTs, including surgical drapes (5,6) and oropharyngeal packing (7). In all reports the oxidizing environment was oxygen (O_2) or O_2 and nitrous oxide (N_2O), gases often present in high concentrations in the oral cavity and pharynx of anesthetized patients.

The oxidant $_{O_2}$ and oxidant $_{N_2O}$ indices of flammability (8,9) are standard and reproducible measurements of flammability are defined as the minimum concentration of oxidant (either O_2 or N_2O) in nitrogen (N_2) diluent that supports a candle-like flame for a given fuel source.

The oxidant $_{O_2}$ and oxidant $_{N_2O}$ indices of ETTs have previously been reported (9). This study is designed to measure the oxidant indices of esophageal stethoscopes, plastic and rubber nasopharyngeal airways, Salem sump nasogastric tubes, and enteric feeding tubes.

Materials and Methods

We tested esophageal stethoscopes (Portex Inc., Wilmington, MA) made of polyvinylchloride (PVC); Salem sump nasogastric tubes (Argyle, St. Louis, MO) made of a PVC base with various plasticizors and colorizors; enteric feeding tubes (Superior Plastic, Cumberland, RI) made of silicone rubber; plastic nasopharyngeal airways (Argyle, St. Louis, MO) made of a PVC base with various plasticizors and colorizors; and rubber nasopharyngeal airways (CR Bard Inc., Murray Hill, NJ) made of latex rubber. The

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Table 1. Oxidant $_{O_2}$ and Oxidant $_{N_2O}$ Indices of Flammability

	Oxidant $_{O_2}$ index (± SD)	99% Confidence interval	Oxidant $_{N_2O}$ index (± SD)	99% Confidence interval
Esophageal stethoscopes	0.218 ± (0.011)	0.020	0.430 ± (0.007)	0.013
Salem sump nasogastric tubes	0.229 ± (0.006)	0.011	0.430 ± (0.003)	0.006
Enteric feeding tubes	0.192 ± (0)	NV*	0.375 ± (0)	NV
Plastic nasopharyngeal airways	0.196 ± (0.006)	0.011	0.415 ± (0.005)	0.010
Rubber nasopharyngeal airways	0.172 ± (0)	NV	0.366 ± (0.004)	0.077

*NV, no variability to third decimal with $n = 5$.

oxidant $_{O2}$ and oxidant $_{N_2O}$ indices were determined using the method described by Wolf and Simpson [9]. Each material was tested five times to determine the oxidant $_{O_2}$ and oxidant $_{N_2O}$ indices of flammability

The flammability of the tested materials in a combination of O_2, N_2O, and N_2 was then determined by flowing O_2 in N_2 corresponding to an O_2 concentration of one-half the oxidant $_{O_2}$ index of flammability for that particular material and introducing N_2O, increasing its concentration while maintaining the concentration of O_2 constant by decreasing the N_2 concentration, until a candle-like flame was propagated. This process was repeated using one-quarter, one-third, two-thirds, and three-quarters of the oxidant $_{O_2}$ index of flammability. Five independent determinations were made at each fraction of the oxidant $_{O_2}$ index, and all of the above was repeated for all of the materials tested. The sequence was then repeated substituting N_2O for O_2, and O_2 for N_2O. Concentrations of N_2O were measured using infrared spectrophotometry and O_2 concentration was determined using a paramagnetic technique (Puritan Bennett, Wilmington, MA).

The oxidant $_{O_2}$ and oxidant $_{N_2O}$ index for each material was determined by averaging each set of five flammability determinations for that material (mean ± SD) and calculating the respective 99% confidence intervals.

Results

The oxidant $_{O_2}$ index of flammability and the oxidant $_{N_2O}$ index of flammability data for all materials tested are summarized in Table 1.

The combination of O_2 and N_2O supported a candle-like flame at one total index (Table 2); i.e., the indices are linearly additive. For example, for esophageal stethoscopes 10.9% O_2, (0.5 oxidant $_{O_2}$ index), 21.5% N_2O (0.5 oxidant $_{N_2O}$ index) and 67.6% N_2 (diluent) supported a candle-like flame. This is true for all combinations of the fractions of the indices measured for all the materials tested so that the graph (Fig. 1) is a straight line. This can be summarized by the following equation, where f = the fraction of the oxidant $_{O_2}$ index for that particular material:

Flammability in $O_2 + N_2O$ = (f) oxidant $_{O_2}$ index + (1−f) oxidant $_{N_2O}$ index; Gas analysis agreed to within ± 1% of flowmeter settings.

Table 2. Minimum Combinations Just Supporting Candle-Like Flame

	%O_2	Fraction oxidant O_2 index	%N_2O	Fraction oxidant N_2O index	%N_2
Esophageal stethoscopes	21.8	1.0	0	0	78.2
	16.4	0.75	10.85	0.25	72.8
	14.6	0.67	14.2	0.33	71.2
	10.9	0.5	21.5	0.5	67.6
	7.2	0.33	28.8	0.67	64
	5.5	0.25	32.3	0.75	62.2
	0	0	43.0	1.0	57.0
Salem sump nasogastric tubes	22.9	1.0	0	0	77.1
	17.2	0.75	10.8	0.25	72
	15.3	0.67	14.2	0.33	70.5
	11.5	0.5	21.5	0.5	67
	7.6	0.33	28.8	0.67	63.6
	5.7	0.25	32.3	0.75	62
	0	0	43.0	1.0	57.0
Enteric feeding tubes	19.2	1.0	0	0	80.8
	14.4	0.75	9.4	0.25	76.2
	12.9	0.67	12.4	0.33	74.7
	9.6	0.5	18.8	0.5	71.6
	6.3	0.33	25.1	0.67	68.6
	4.8	0.25	28.1	0.75	67.1
	0	0	37.5	1.0	62.5
Plastic nasopharyngeal airways	19.6	1.0	0	0	80.4
	14.7	0.75	10.4	0.25	74.9
	13.1	0.67	13.7	0.33	73.2
	9.8	0.5	20.8	0.5	69.4
	6.5	0.33	27.8	0.67	65.7
	4.9	0.25	31.1	0.75	64
	0	0	41.5	1.0	58.5
Rubber nasopharyngeal airways	17.2	1.0	0	0	82.8
	12.9	0.75	9.2	0.25	77.9
	11.5	0.67	12.1	0.33	76.4
	8.6	0.5	18.3	0.5	73.1
	5.7	0.33	24.5	0.67	69.8
	4.3	0.25	27.5	0.75	68.2
	0	0	36.6	01.0	63.4

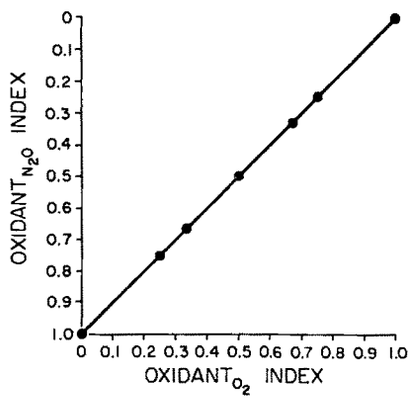

Figure 1. The fraction of the oxidant $_{O_2}$ index plotted against the corresponding fraction of the oxidant $_{N_2O}$ index.

Discussion

The oxidant $_{O_2}$ index of flammability, a standard widely accepted in the plastics industry (8–10), is a measure of the ability of an oxidant to propagate a flame for a given fuel and is independent of the ignition source. Ignition sources in the clinical setting include laser beams, electrocautery, and high speed drills. This study measured the flammability of esophageal stethoscopes, Salem sump nasogastric tubes, enteric feeding tubes, and plastic and rubber nasopharyngeal airways in O_2/N_2, $O_2/N_2O/N_2$, and N_2O/N_2. Although esophageal stethoscopes, Salem sump nasogastric tubes, and plastic nasopharyngeal airways are all made with a PVC base, they contain different plasticizors and colorizors in varying percentages (exact information was not made available to us by the various manufacturers for proprietary reasons). This accounts for their differences in appearance, consistency and flammability characteristics.

All tested materials are flammable in the range of oxygen concentrations common to the clinical setting (Table 1). Rubber and plastic nasopharyngeal airways are flammable in O_2 concentrations (in N_2) less than the 21% concentration present in ambient air (17.2 and 19.6%, respectively). Similarly, enteric feeding tubes are flammable in an O_2 concentration of 19.2% (in N_2). While esophageal stethoscopes and Salem sump nasogastric tubes are flammable in O_2 concentrations greater than the concentration of O_2 in ambient air (21%), they are below the range of O_2 concentrations considered acceptable in anesthetic practice.

The oxidant $_{N_2O}$ indices of flammability confirm the concept of N_2O as an oxidizing agent, and use of the oxidant $_{N_2O}$ index as a useful measure of flammability. The combination of the three gases (O_2, N_2O, N_2) again (9) revealed the oxidant $_{O_2}$ and oxidant $_{N_2O}$ indices to be linearly additive and therefore confirms the concept of avoiding N_2O as a diluent for O_2 in situations where an ignition source is in close proximity to a fuel. We therefore recommend avoidance of the use of these potentially flammable materials in close proximity to an ignition source.

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Clinical Reports

ECG Artifact Simulating Supraventricular Tachycardia During Automated Percutaneous Lumbar Discectomy

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Key Words: HEART, ELECTROCARDIOGRAPHY—artifact. SURGERY, NEUROLOGIC—nucleotome.

Automated percutaneous lumbar discectomy (APLD) is a relatively new procedure used to treat herniated lumbar discs. Although the procedure is always performed using local anesthesia, it is the practice in our institution to have an anesthesiologist stand by to monitor patients undergoing the procedure. Using fluoroscopic guidance, a specially designed trocar is inserted into the disc space and the herniated nucleus is removed by a suction cutting probe. We report a case of artifactual supraventricular tachycardia occurring during automated percutaneous lumbar discectomy.

Case Report

A 35-year-old man, previously healthy, presented complaining chiefly of lower back pain with radiation to the lateral aspect of the left leg. The pain developed suddenly when the patient lifted a heavy pallet while working. A 4-week course of rest, muscle relaxants, and anti-inflammatory drugs failed to relieve the pain.

On physical examination, positive findings included depressed Achilles reflex and a positive straight leg lift at 40° on the left. A myelogram and computed tomography scan revealed the herniated lumbar disc at the L-4 level, without free fragments. Therefore, it was decided to perform automated percutaneous lumbar discectomy on the patient.

In the operating room the patient was placed in the right lateral decubitus position. He was monitored with electrocardiogram (Physio-control VSM-1), blood pressure, and precordial stethoscope. An intravenous infusion was begun. The patient was given 50 μg fentanyl and 3 mg midazolam, intravenously. The lumbar area was cleansed with povidone–iodine solution. After infiltration of the skin and subcutaneous tissues with 1% lidocaine, the APLD trocar was placed into the fourth lumbar disc. When x-ray evidence of successful placement was obtained, the nucleotome was activated at a frequency of 180/minute and resection of the disc material was begun. The patient rested comfortably and remained hemodynamically stable during the first 15 minutes of resection, when the electrocardiogram revealed sudden onset of what appeared to be supraventricular tachycardia at a rate of 180 beats/min (Fig. 1). The patient was asymptomatic, and manual palpation of the pulse revealed his heart rate to be 80 beats/min. The resection was halted, revealing no ECG signal on lead II and normal sinus rhythm on lead I (Fig. 2). Checking lead placement on all the electrodes, we found the left leg lead had lost contact. After being reapplied, there was a return to normal sinus rhythm on the electrocardiogram (Fig. 3).

To test the hypothesis that a loose electrocardiographic lead could have caused the artifact, one ECG patch was removed and re-applied so that only partial contact with the gel of the patch was made with the patient's skin. When the resection continued, the artifactual supraventricular tachycardia recurred. By improving patient electrode contact (applying manual pressure to the lead), the normal sinus rhythm was again seen.

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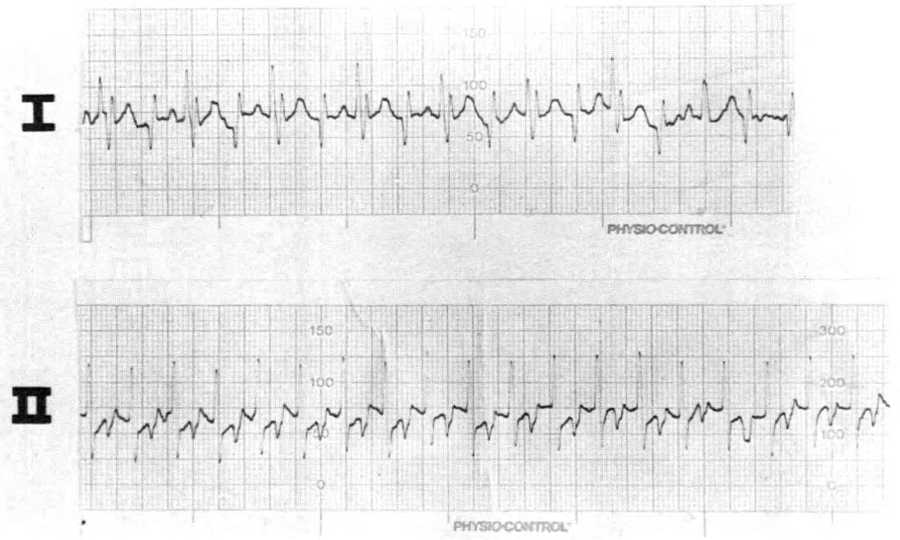

Figure 1. Electrocardiogram tracing of leads II and I revealing apparent tachyarrhythmia at a rate of 180 beats/min.

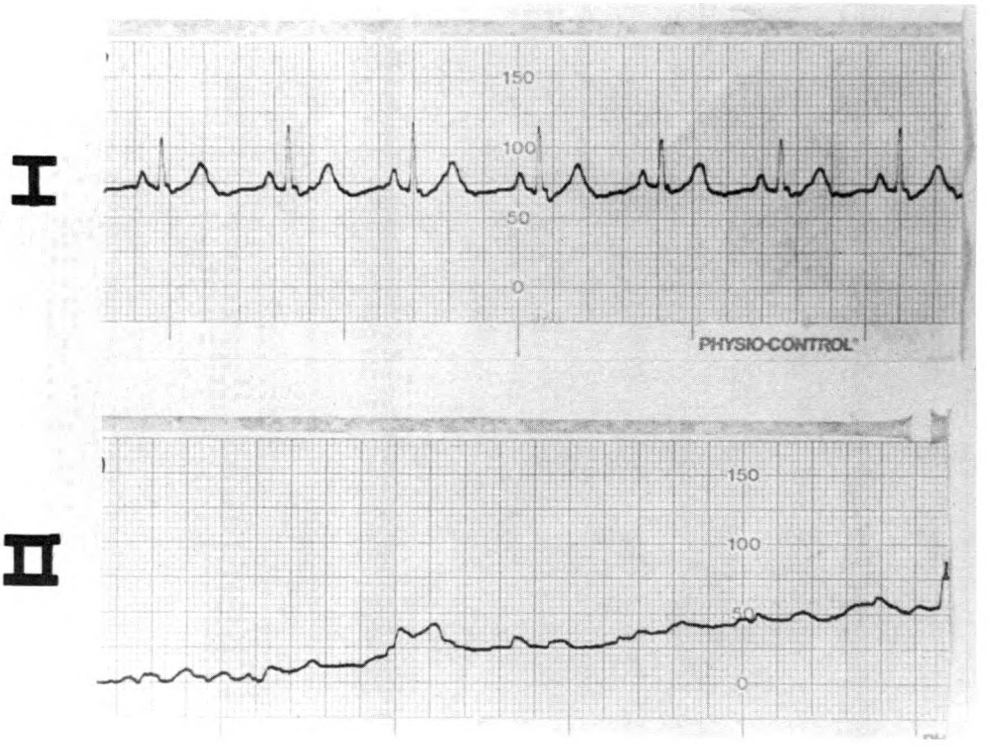

Figure 2. Rhythm strips obtained after turning off the APLD resecting nucleotome. Note that lead II is normal, and lead I is flat, indicating disconnection of the left arm electrode.

Discussion

Automated percutaneous lumbar discectomy is different from standard lumbar surgery because there is no muscle dissection, bone removal, or nerve manipulation. Thus, most complications that occur with open surgery are eliminated with automated percutaneous lumbar discectomy. Percutaneous discectomy has been suggested as an alternative to lumbar discectomy for about four years and is now preferred by some to the open procedure or to chemonucleolysis. The patients can return home relatively quickly after this procedure, and indeed, APLD has been performed on outpatients (1–3). There are few hazards to this procedure, and patients are continuously monitored during nucleotome insertion and disc resection for nerve injury, puncture of vital structures, or blood loss. However, there have been

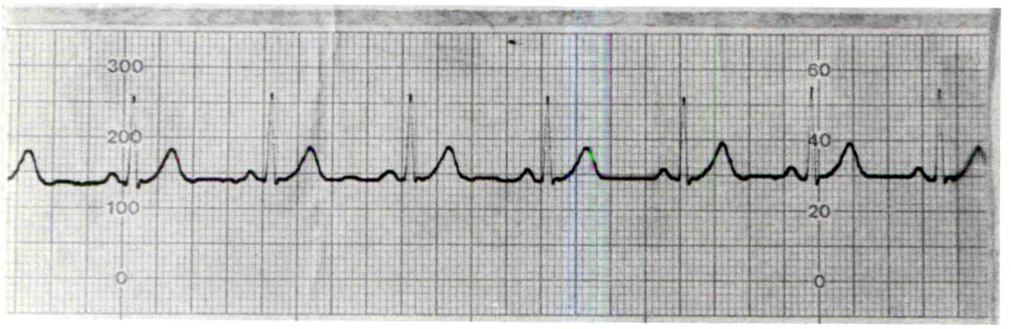

Figure 3. Electrocardiogram lead II after re-connecting the left arm electrode during APLD resection.

no case reports describing ECG artifacts during APLD.

During APLD, a nucleotome is placed through a trocar into the lumbar disc. The nucleotome probe is blunt ended, with a single side cutting port. The probe head is very similar to a guillotine cutting instrument; the cutting blade inside the nucleotome is pneumatically driven across the side port and thereby resects the disc material. The resected disc material is aspirated through the center of the cutting port while continuous saline irrigation is achieved through the nucleotome itself.

Our patient had a sudden onset of ECG evidence of supraventricular tachycardia. The ECG tracing, seen in Figure 1, suggested supraventricular tachycardia. The tachycardia could have been associated with the transmission of every third beat on the peripheral pulse. However, auscultation of the precordium also indicated an apical rate that was equal to the peripheral rate, about 80 beats/min. By stopping the nucleotome (Fig. 2) we found that the ECG findings were due to mechanical interference from the automatic percutaneous lumbar discectomy.

Electrocardiogram artifacts are most commonly caused by poor electrode contact. Muscle fasciculations or contractions, patient movement, or electromechanical interference are also possible causes of artifactual ECG findings (4). Because the automated percutaneous lumbar discectomy nucleotome is pneumatically rather than electrically driven, electrical contact or passage of current through the patient is unlikely, and mechanical interference was the most probable cause of the artifactual dysrhythmia. The mechanical interference, which was an artifact of the loose electrocardiographic lead, resulted in an ECG rate equal to the frequency of nucleotome movements. This is analogous to the artifact reproducible on many ECG monitors by tapping the ECG leads with one's hand. Any movement of ECG wires (by the patient or from external sources) may be translated into apparent electrical energy on the oscilloscope. In our case, reconnecting the left arm electrode gave a normal ECG during use of the nucleotome (Fig. 3).

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Benzocaine-Induced Methemoglobinemia in an Adult: Accuracy of Pulse Oximetry with Methemoglobinemia

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Key Words: ANESTHESIA, LOCAL—benzocaine. BLOOD, methemoglobinemia. OXYGEN, MEASUREMENT—pulse oximetry.

Benzocaine-induced methemoglobinemia has been reported frequently in infants (1–4) and somewhat less frequently in adults (5–7). In these reports the patients presented with cyanosis. The following is a case report of significant methemoglobinemia after benzocaine and its effects on the oxygen saturation as reported by a pulse oximeter.

Case Report

A 52-year-old man with squamous cell cancer of the retromolar trigone region was scheduled for a radical neck dissection and partial mandibulectomy. His history showed a possible inferior wall myocardial infarction 15 years previously, with no subsequent chest pain. He consumed large amounts of alcohol, had alcohol-related seizures, and smoked two packs of cigarettes per day. He took 100 mg of phenytoin three times daily.

Because of concern about our ability to intubate this patient, we gave him topical 2% viscous lidocaine, 5 ml, followed by 2 1-second sprays of Cetacaine (14% benzocaine, 2% tetracaine, and other ingredients). Awake laryngoscopy correctly predicted an easy intubation, and we induced anesthesia in a routine intravenous manner. Over the next hour the pulse oximeter (Ohmeda Biox 3700) displayed a progressive decrease in oxygen saturation, from 99% down to 94%, and eventually to the mid-80s after 3 hours. Arterial blood gas with an inspired oxygen concentration of 50% continued to show oxygen tensions of greater than 200 mm Hg with a calculated oxygen saturation of greater than 98%. However, the blood looked dark, even after agitation in room air.

Analysis of the blood by a co-oximeter (Instrumentation Laboratory 482) revealed 26% methemoglobin (MetHb), 2.5% carboxyhemoglobin, 71% oxyhemoglobin (SaO_2), and a total hemoglobin (Hb) of 16 gm/dl. Methylene blue 1.5 mg/Kg was given intravenously. Thirty minutes later MetHb was 11%, and oxygen saturation by pulse oximetry (SpO_2) was still 84%. By 60 minutes after methylene blue was given MetHb was 3.9%, and SpO_2 was 96%.

This patient's blood pressure and heart rate were within the normal range throughout the anesthesia and operation. The maximum base deficit was 3.7 meq/L on a sample drawn shortly before methylene blue was given. The patient awoke without sequelae and had an unremarkable postoperative course. Two weeks after the operation MetHb level was normal.

Discussion

Methemoglobinemia is formed normally in the body because small amounts of the ferrous iron (Fe^{++}) in Hb are continuously oxidized to the ferric (Fe^{+++}) form, which cannot carry oxygen or carbon dioxide. The red cells' defense against accumulated MetHb is primarily MetHb NADH reductase, which is responsible for 95% of in vivo reduction of the ferric iron MetHb to form normal Hb (8). This system normally keeps the MetHb level at less than 1%.

Congenital methemoglobinemia is caused either by insufficient production of the enzyme MetHb NADH reductase or by abnormal Hb (Hb M) variants that are stable with the iron in the ferric form, and thus cannot be reduced. Acquired methemoglobinemia can be associated with toxic shock, or can be drug-induced.

A partial list of drugs implicated in causing methemoglobinemia is presented in Table 1 (8,9). These

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Table 1. Agents Implicated in Acquired Methemoglobinemia

Acetanilid
Aminobenzenes
Aniline dyes
Local Anesthetics
Prilocaine
Benzocaine
Lidocaine
Procaine
Naphthalene
Nitrites (or Nitrates)
Amyl nitrate
Sodium nitrite
Nitroglycerin
Food additives
Well water high in nitrates
Nitrobenzenes
Phenacetin
Phenazopyridine (Pyridium)
Primaquine
Resorcinol
Sulfonamides

drugs may overwhelm the normal defense against oxidants and produce alarming levels of MetHb. Although cyanosis may appear with levels as low as 15%, acquired methemoglobinemia is only rarely symptomatic when levels are below 20%. Lethargy, dizziness, and headache may present with levels between 30–40%, and levels above 70% can be fatal (8,9).

When a portion of the hemoglobin has been oxidized to MetHb, the physiologic effect is more pronounced than a mere reduction of the total Hb by that fraction of MetHb would be. This is because MetHb increases the affinity of normal Hb for oxygen, thereby hindering oxygen release in the tissues (8,9). Once the offending drug has been removed, the body's natural defense system will reduce MetHb within 24–72 hours.

Methylene blue, given intravenously 1–2 mg/kg over 5 minutes, acts as a cofactor in the transfer of an electron from NADPH to ferric iron in a reaction catalyzed by MetHb NADPH reductase. In this reaction methylene blue is first reduced to leukomethylene blue, which then reduces MetHb to normal Hb. There is no endogenous cofactor to act as an electron acceptor for NADPH, so that the reaction catalyzed by NADPH MetHb reductase is normally responsible for, at most, 5% of the reduction of MetHb. However, with the addition of methylene blue, methemoglobinemia should be resolved within one hour. If not, the dose of methylene blue may be repeated. The total dose should not exceed 7 mg/kg because high levels may directly oxidize normal Hb to cause methemoglobinemia (8,9).

Methylene blue should not be given to patients with glucose-6-phosphate dehydrogenase deficiency, because the hexose monophosphate shunt regenerates NADPH. With deficient NADPH regeneration, methylene blue may cause hemolytic anemia (8,9). Methylene blue will also be ineffective in the presence of Hb M variants.

Normal MetHb levels postoperatively and the efficacy of methylene blue rule out HbM as the cause of methemoglobinemia in our patient. Assay of our patient's blood for MetHb NADH reductase yielded 22.0 IU/g Hb, with the normal range being 11–27 IU/g Hb, so that our patient would not be expected to be abnormally susceptible to oxidant stresses.

Our patient received two drugs, other than benzocaine, that have been reported to cause methemoglobinemia. There is one case report in the English language literature of phenytoin-induced methemoglobinemia involving a newborn (10). Although lidocaine-induced methemoglobinemia has been reported twice (11,12), it is unlikely to cause significant methemoglobinemia in the usual clinical doses (13).

Cetacaine is a mixture containing 14% benzocaine and 2% tetracaine, among other ingredients. Of these ingredients, benzocaine has often been implicated as causing methemoglobinemia (1–7). Benzocaine is usually poorly absorbed after topical application but the manufacturer warns against its use on inflamed or denuded tissue. The recommended dosage of Cetacaine is 1 second of spray from the Jetco cannula. We gave about 2 seconds of spray, which upon later investigation yielded nearly 1 ml of liquid. The oral mucosa of our patient was probably altered by his cancer so that a larger than usual amount of benzocaine may have been absorbed. The oxidant stress of the absorbed benzocaine may have been enhanced by the previously administered lidocaine and the phenytoin that the patient was taking chronically. Furthermore, some of the Cetacaine spray may have been inhaled into the trachea. Benzocaine given intratracheally can rapidly induce very high methemoglobin levels, as shown by Barker et al. (14). In this animal study, MetHb levels of 60% or more were induced by injecting aerosolized benzocaine through an endotracheal tube. This method proved more rapid and reliable in producing methemoglobinemia in dogs than either intravenous prilocaine or nitrates.

We were first alerted to the presence of methemoglobinemia by the decrease in SpO_2. All vital signs and laboratory values were otherwise normal. Our patient probably would have successfully reduced the high levels of MetHb without therapy in 24–72 hours. An almost universal finding in the reported cases of methemoglobinemia is normal oxygen tension by arterial blood gases and high calculated oxygen saturation. Calculated oxygen saturation as-

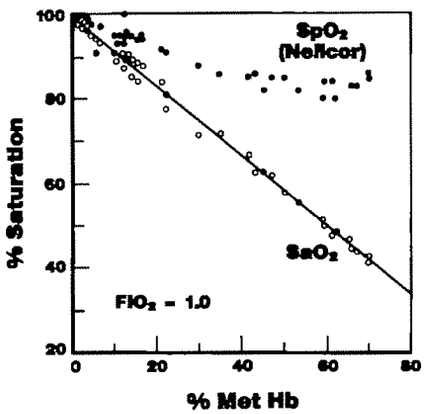

Figure 1. SpO_2 (Oxygen saturation by pulse oximeter (Nellcor)) and SaO_2 (Percent oxyhemoglobin by IL-282 Co-Oximeter) vs MetHb at FI_{O_2} = 1.0. Linear regression shown for Sao_2. Reproduced with permission from Barker SJ, et al., Anesthesiology 1987;67:A171.

sumes the presence of only normal Hb existing in either the oxygenated or deoxygenated state.

Although the pulse oximeter (Ohmeda Biox 3700) alerted us to the presence of abnormal hemoglobin, the accuracy of the SpO_2 from this monitor was seriously affected by the presence of MetHb. Barker et al. showed that methemoglobinemia interfered with the accuracy of pulse oximetry in dogs (14) as shown in Figure 1. They found that with increasing levels of MetHb the SpO_2 approached 85%, and continued to read in the mid-80s over a wide range of SaO_2 by co-oximeter for all MetHb levels from 30–65% of total Hb. Our pulse oximeter similarly reported SpO_2 values in the mid-80s when MetHb was 26%.

Another recently reported case has documented low SpO_2 readings (92–93%) despite a PO_2 of 587 mm Hg because of a 5% MetHb level (15). Oxyhemoglobin by IL 282 was 92.8% so that in this case the SpO_2 appeared to be "accurate." That author speculated upon the inaccuracy in SpO_2 that would result from higher levels of MetHb, which in fact were reported by Barker et al. in dogs. Our report is the first confirmation of this experimental data in a patient.

The pulse oximeter measures the light absorbance of tissue at two wavelengths, one in the red and the other in the near infrared range. Because it measures the pulsatile component of "pulse-added absorbance", the pulse oximeter is sensitive specifically to arterial blood. The software in the machine then translates the ratio of the pulse-added absorbances of these two wavelengths into an oxygen saturation (SpO_2) using data collected from volunteers. Methemoglobin has a high absorbance at both wavelengths, tending to drive the ratio of absorbances (R) toward one. An R value of 1 corresponds to an SpO_2 of 85%; thus high MetHb levels will drive SpO_2 toward 85% regardless of oxygen tension.

There have been other reports of abnormal conditions that influence accuracy of pulse oximeters. Methylene blue, indocyanine green, and indigo carmine (listed in decreasing amount of interference) have been reported to cause spuriously low pulse oximeter readings (16,17). Carboxyhemoglobin, which is bright red, apparently is interpreted by pulse oximetry as though it were mostly oxyhemoglobin (18). Indeed, any substance with a high absorption coefficient in either of the two wavelengths used in pulse oximetry will be likely to cause spurious oxygen saturation readings.

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Rectal Methohexital for Induction of Anesthesia in Children with and without Rectal Aspiration after Sleep:

A Pharmacokinetic and Pharmacodynamic Study

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Key Words: ANESTHESIA—pediatric.
ANESTHETIC TECHNIQUES—induction.
ANESTHETICS, INTRAVENOUS—methohexital.

The use of rectally administered methohexital is a widely accepted anesthetic induction technique in pediatric patients. Prolonged emergence from anesthesia is anticipated after procedures of short duration. This study was designed to investigate the hypothesis that removing as much unabsorbed methohexital as possible after induction might shorten recovery time.

Methods and Materials

After obtaining institutional approval and written, informed consent from parents, 20 day-surgery patients scheduled for tonsillectomy and/or adenoidectomy were studied. No premedication was used. For induction of anesthesia all patients received 25 mg/kg of a 2.5% methohexital solution, administered by a research anesthesiologist not involved in the patient's care, over a 1-minute period via a 14-French gauge red rubber catheter introduced 5 cm into the rectum and left in situ after completion of methohexital injection. An independent observer measured the time from end of injection of the methohexital to the onset of sleep, which was defined as loss of consciousness, absence of purposeful movement when unstimulated, and unresponsiveness to verbal stimuli. The independent observer left the operating room after the patient was asleep and was unaware as to whether or not the rectum was suctioned during withdrawal of the catheter. The observer returned at the end of the procedure for the final observations.

Patients were randomly assigned to one of two groups. After loss of consciousness in group 1, the catheter was withdrawn from the rectum by the researcher with constant suctioning by syringe to remove as much unabsorbed methohexital solution as possible. The volume of the aspirate was noted and a sample saved for analysis. After loss of consciousness in group 2, the catheter was removed without suctioning. The independent observer and anesthesiologist caring for the patient were unaware of the patient's group assignment. Anesthesia then proceeded identically in both groups. Intubation was performed and halothane, nitrous oxide, and oxygen were administered, followed by maintenance of anesthesia with 60% nitrous oxide in oxygen and 1.5–2.5% isoflurane. No narcotics or muscle relaxants were used. After completion of surgery the nitrous oxide and isoflurane were discontinued, and the patient breathed 100% oxygen until extubation. The elapsed time from the discontinuation of the anesthetic to each of the following events was noted by the same independent observer: 1) return of spontaneous movement, 2) extubation, and 3) spontaneous eye opening. Extubation was performed when adequate spontaneous ventilation, return of protective airway reflexes, and cough without subsequent breath holding were present. The duration of anesthesia was defined as the time between the completion of administration of the methohexital and the discontinuation of the nitrous oxide and isoflurane.

An intravenous cannula was inserted after loss of

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consciousness and 2 ml of blood taken for methohexital analysis at 10, 15, 20, 40, 90, and 120 minutes after administration of the methohexital. The blood samples were centrifuged at 3000 rpm for 10 minutes at −10°C and the plasma stored at −30°C until analysis. Samples of the injected solutions and rectal aspirates were labeled only with the patient's hospital number and stored in a similar manner until analysis.

High resolution capillary gas chromatography, in conjunction with a mass spectrometer as ion detector, was used to analyze the methohexital concentration in plasma samples (1). All samples were run in triplicate. The sensitivity of the method was less than 1 ng/ml, and the coefficient of variance was 4%. Prior to extraction and analysis, the 2.5% injected solutions of methohexital and the aspirated rectal solutions were volumetrically diluted to within the range 100–3000 ng/ml. New calibration curves for aqueous solutions of methohexital were obtained from the standard solutions for these samples. The coefficient of variance in these cases was 6–12%.

Pharmacokinetic analysis was done using a compartmental independent method (2). The area under the plasma concentration curve (AUC) was determined for each patient by means of the linear trapezoid rule for the ascending portion of the curve and the logarithmic trapezoid rule for the descending part of the curve. The apparent methohexital clearance was determined for each patient using: clearance = (F·dose)/AUC. However, the bioavailability (F) is unknown. Therefore the apparent clearance is defined as: clearance/F = dose/AUC. The half-life of plasma methohexital was calculated in each patient by means of regression analysis based on the 40, 90, and 120 minute methohexital blood concentrations whenever possible. Six patients in the suctioned group and eight patients in the non-suctioned group qualified for this method. Correlation coefficients (r) were also calculated. In all other patients the half-life was derived from the last two plasma concentrations.

Statistical analysis was by Student's t-test with statistical significance assumed with $P < 0.05$.

Results

There were ten patients in each group with no significant differences in age, weight, duration of anesthesia or time to onset of sleep found between the two groups (Table 1). All patients were ASA Physical Status 1 or 2. The mean time to onset of sleep for all 20 patients was 7.3 minutes (range, 4–13 minutes). There was no distress associated with leaving the catheter in situ, and no child expelled any of the methohexital.

Table 1. Demographic and Anesthetic Data in Suctioned and Non-suctioned Groups*

	Non-suctioned	Suctioned	P-value
Age (months)	35 ± 10	33 ± 9.9	0.6
Weight (kg)	13.7 ± 4	14 ± 2.3	0.8
Duration of anesthesia (min)	33 ± 7.2	34 ± 11.7	0.8
Time to sleep (min)	7.8 ± 2.9	6.9 ± 2.1	0.4

*Results are expressed as mean ± SD. n = 10 in both groups.

Table 2. Data on Recovery from Anesthesia in Suctioned and Non-suctioned Groups*

Elapsed time	Non-suctioned	Suctioned	P-value
To extubation (min)	16.4 ± 8 0	8.1 ± 3.8	0.006
To movement (min)	15.3 ± 6 3	6.1 ± 3.7	0.0001
To eye opening (min)	36.4 ± 13.2	21.4 ± 11.1	0.01
In recovery room (min)	57.5 ± 17.8	58 ± 17.5	0.9

*Results are expressed as mean ± SD. n = 10 in both groups.

Table 3. Mean Plasma Methohexital Blood Levels in Suctioned and Non-suctioned Groups at Times Studied*

Time (min)	Non-suctioned (μg/ml)	Suctioned (μg/ml)	P-value
10	7.50 ± 4.4	5.27 ± 1.344	0.1127
15	5.76 ± 3.641	4.88 ± 2.561	0.2664
20	5.33 ± 3.435	4.04 ± 1.64	0.1513
40	3.64 ± 2.189	2.16 ± 0.936	0.0328
90	1.99 ± 1.393	0.71 ± 0.271	0.0077
120	1.20 ± 0.789	0.51 ± 0.23	0.0218

*Results are expressed as mean ± SD.

The mean volume of solution recovered by aspiration after loss of consciousness in group 1 was 59% (SD, ±11%) of the administered volume. Analysis of the aspirated solutions for methohexital content showed that a mean of 45% (SD ± 13%) of the administered dose had been recovered by aspiration.

The results for recovery from anesthesia are shown in Table 2; times to extubation, return of spontaneous movement, and spontaneous eye opening were significantly lower in the suctioned group.

The results of the measurements of plasma methohexital levels are listed in Table 3; plasma levels of methohexital were significantly lower in the suctioned group 40, 90, and 120 minutes after administration of the rectal methohexital. Calculated pharmacokinetic parameters and associated P-values are shown in Tables 4, 5, and 6. Calculated half lives must be regarded as tentative where only two plasma levels were available.

Discussion

Peak plasma levels of methohexital and time to onset of sleep agree with the other studies that have used

Table 4. Calculated Pharmacokinetic Parameters in Suctioned Group

Patient	Apparent clearance ($ml \cdot kg^{-1} \cdot min^{-1}$)	Apparent half life (min)	r	AUC ($\mu g \cdot min \cdot ml^{-1}$)
1	94.4	36.6	0.9840	223.4
2	145.5	43.8	0.9540	141.0
3	117.7	11.2	*	117.2
4	125.5	28.1	*	135.4
5	75.9	27.6	0.9975	236.7
6	66.4	31.4	*	276.6
7	69.4	28.8	0.9999	228.6
8	40.1	34.2	0.9857	415.2
9	54.4	54.5	*	310.6
10	30.8	35.4	1.000	272.2

*Half-life determined from the last two plasma concentrations. All others determined from 40, 90, and 120 minute plasma concentrations.

Table 5. Calculated Pharmacokinetic Parameters in Non-suctioned Group

Patient	Apparent clearance ($ml \cdot kg^{-1} \cdot min^{-1}$)	Apparent half life (min)	r	AUC ($\mu g \cdot min \cdot ml^{-1}$)
11	66.9	50.4	0.9932	374.0
12	89.5	35.4	0.999	279.5
13	64.7	31.8	0.9952	386.4
14	220.4	32.4	0.9799	113.5
15	84.9	57.4	*	294.3
16	39.5	131.4	0.9392	633.0
17	30.4	28.8	0.9547	821.2
18	50.5	79.2	0.9407	495.3
19	67.9	61.8	*	368.1
20	24.9	75.6	0.9779	1004.5

*Half-life determined from the last two plasma concentrations. All others determined from 40, 90, and 120 minute plasma concentrations.

Table 6. Apparent Clearance, Apparent Half-Life, and Area under the Curve in the Suctioned and Non-suctioned Groups*

Calculated Parameter	Non-suctioned	Suctioned	P-value
Apparent clearance ($ml \cdot kg^{-1} \cdot min^{-1}$)	74.0 ± 55.8	82.0 ± 37.9	0.355
Apparent half-life (min)	58.4 ± 31.5	33.2 ± 11.3	0.014
AUC ($\mu g \cdot min \cdot ml^{-1}$)	476.9 ± 270	235.7 ± 90.7	0.0077

*Results are expressed as mean ± SD.

25 mg/kg of rectal methohexital, either as a 10% or a 2% solution (3–5).

The time spent in the recovery room was virtually identical in both groups at a mean of 57–58 minutes. In our hospital, children who have been intubated must stay a minimum of 45 minutes. These times spent in the recovery room are also comparable to other reports after rectal methohexital (4,5).

Rectal aspiration was effective in reducing the apparent plasma half-life of rectally administered methohexital. It also decreased AUC significantly. Rectal aspiration of methohexital decreases the amount of drug available for absorption from the rectum as well as reducing the time the rectal mucosa is exposed to the drug. The reservoir of methohexital remaining in the rectum in the non-suctioned group acts like a sustained-release dosage form of methohexital, increasing the apparent half-life of the drug through continued absorption.

The times at which plasma levels of methohexital were significantly lower in the suctioned group, between 40 and 120 minutes after administration, correspond in this study to the times at which surgery was ending and clinical recovery from anesthesia started. We also found significant improvements in the clinical indices of recovery from anesthesia during this period.

Our conclusion from this study is that 45% of the administered dose of rectal methohexital can be recovered by aspiration after loss of consciousness. This results in significantly lower blood levels of methohexital between 40 and 120 minutes after administration and significantly faster clinical recovery from anesthesia, but does not decrease efficacy of rectal methohexital for induction of general anesthesia in children. With this technique, the advantages of rectal induction of anesthesia with methohexital are retained while the disadvantage of prolonged recovery is eliminated.

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Continuous Subpleural-Paravertebral Block in Acute Thoracic Herpes Zoster

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Key Words: ANESTHETIC TECHNIQUES, regional: sub-pleural paravertebral block. INFECTION, herpes zoster. PAIN, herpes zoster.

Numerous nerve block techniques have been used for the management of pain associated with acute herpes zoster (HZ). The first nerve block to be described for this purpose consisted of repeated paravertebral blocks (1). A continuous technique that circumvents intermittent injections would seem to be advantageous in this situation. However, few techniques provide effective continuous unilateral thoracic analgesia. Epidural block, the technique of continuous nerve block used most widely to treat thoracic HZ, provides bilateral segmental analgesia. A novel approach to unilateral thoracic analgesia, continuous subpleural-paravertebral block, is presented in a case of acute thoracic HZ.

Case Report

A 65-yr-old man with a history of metastatic prostatic carcinoma presented with nausea, vomiting, dehydration, and a T5 dermatomal rash consistent with acute thoracic HZ. Zoster infection was later confirmed with Tzanck smear and viral cultures. The patient had developed a sharp, burning pain in the area of the left T5 dermatome about 8 to 9 days before admission. This was followed by the appearance of the characteristic vesicular, erythematous rash of HZ. Treatment with intravenous acyclovir was initiated, and, after informed written consent for the procedure was obtained, a modified continuous intercostal block, continuous subpleural-paravertebral block, was performed.

The patient was placed sitting upright with his legs over the edge of the bed. With the posterior rib angle as a landmark, the fifth rib on the left was palpated as far medially as possible (i.e., in this case, approximately 5 cm from the midline, posteriorly). Under aseptic conditions, the skin in this area was infiltrated with 2 percent lidocaine. A 16 gauge Racz® epidural needle (Medical Evaluation Devices and Instruments Corp., Gloversville, NY) was introduced at 90° to the skin in all planes, with the bevel facing superiorly, to contact the underlying left fifth rib. The needle was then redirected medially (i.e., about 50–60°) and cephalad, and advanced about 3 mm to pass over the superior aspect of the rib. The needle stylet was removed, and a syringe with extension tubing filled with preservative-free normal saline was attached. The needle was then advanced using a two-person, loss-of-resistance technique (2). A definite loss of resistance was elicited with the passage of the needle into the intercostal space. At this point, the needle was advanced an additional 5 mm to insure placement medially in the intercostal space. Following a negative aspiration, and with the bevel of the needle redirected medially, a Racz Tun-L-Cath® (Medical Evaluation Devices and Instruments Corp., Gloversville, NY) epidural catheter was advanced 3 to 4 cm into the intercostal space medially and the needle withdrawn. Next, 5 ml of 2 percent lidocaine was injected through the catheter. Ten minutes later, analgesia to pinprick and temperature discrimination was present in a T4-T9 dermatomal distribution on the left and there was marked decrease in pain in the area of the rash. On chest radiograph, the radiopaque catheter tip was found to be at T3 (Fig. 1). The catheter was directed in a medial-cephalad orientation anatomically consistent with placement initially in the intercostal space, communicating with the subpleural-paravertebral space. Injection of 6 ml Isovue 300® contrast (Squibb Diagnostics, New Brunswick, NJ) through the catheter resulted in vertical spread in a paramedian band across several intercostal levels, i.e., T3-T8 (Figs. 2 and 3). This appeared to

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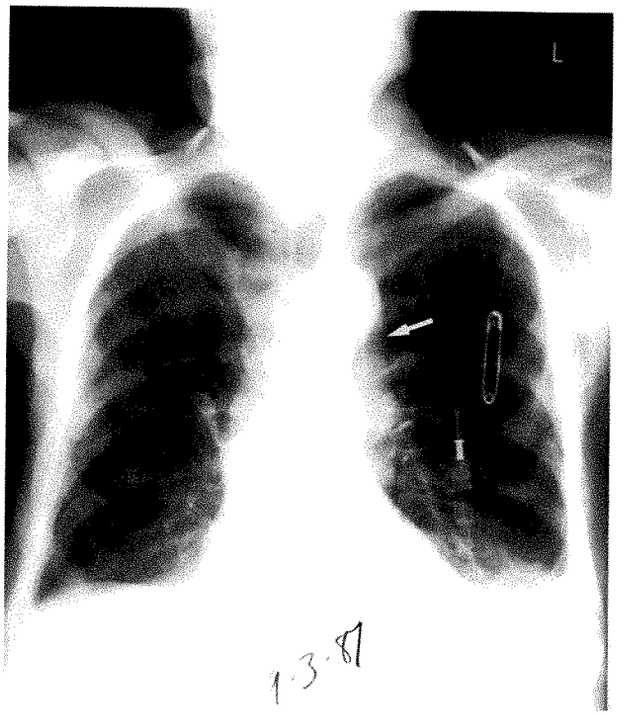

Figure 1. Chest x-ray (PA view) with arrow pointing to the catheter tip. Note the paravertebral location of the catheter tip at the level of the T3 vertebral body.

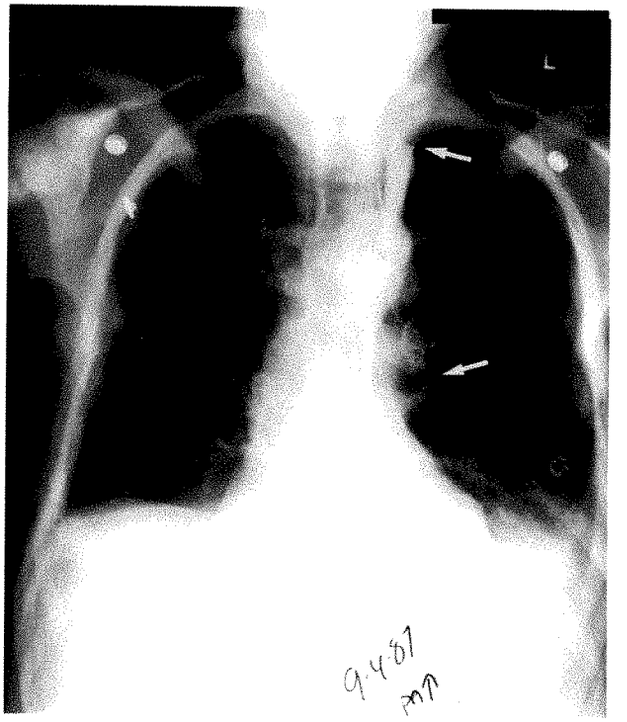

Figure 2. Chest x-ray (PA view) with arrows showing the margins of spread of contrast following injection of contrast medium through the catheter. Note the paravertebral location with spread between the T3-T8 vertebral bodies.

confirm subpleural-paravertebral localization. A continuous infusion of 0.25% bupivacaine was started at a rate of 5 ml/hr via the catheter, with the infusion continued for 4 days thereafter. Analgesia in the area of the rash continued throughout maintenance of the infusion, with decreased sensation to pinprick and temperature discrimination on the left. The rash of HZ progressed rapidly from the vesicular stage to the drying-crusting stage observed with healing.

Discussion

A variety of nerve block techniques have been used to treat the acute phase of HZ. In 1938, Rosenak reported that repeated paravertebral blocks of sympathetic ganglia relieved the pain of acute HZ, and also noted that the blocks appeared to hasten healing of the rash (1). The observation that early sympathetic blockade can relieve pain, enhance healing, and prevent postherpetic neuralgia in acute HZ has been supported by a number of studies (1,3–5).

In 1979, Eason and Wyatt (6) described a continuous catheter technique to inject a local anesthetic solution into the paravertebral space. They described several cases of multisegmental, unilateral analgesia in postthoracotomy patients. More recently, Conacher and Kokri (7), using a continuous paravertebral technique, injected contrast medium into catheters placed into patients who had undergone thoracic operations. They found that in patients in which contrast medium spread paravertebrally, injection of local anesthetic was associated with unilateral loss of pinprick and temperature discrimination in a wide unilateral dermatomal pattern.

Repeated intercostal nerve blockade has been well-established as a technique for relief of pain in the thoracic area. Use of an intercostal catheter provides continuous analgesia with repeated injections of local anesthetic (8–11). The mode of spread of local anesthetic and mechanism of action of multisegmental intercostal nerve blockade following injection into a single intercostal space, however, continues to be debated (10–16). Spread of local anesthetic medially to the paravertebral space has been advocated as a mechanism in some reports (11,16).

In attempting the technique of intrapleural catheterization at this institution, using the method of Rocco et al. (17), it was noted that, by orienting the introducing needle medially at a position medial to an upper thoracic rib angle (i.e., about 4 to 5 cm from the midline posteriorly), pleural puncture was consistently avoided. This is because of the relative parallel orientation of the needle with the pleural surface at

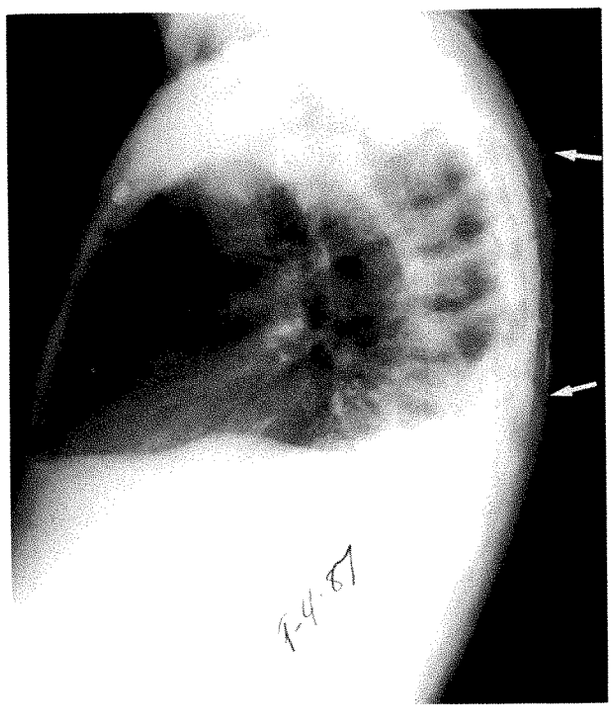

Figure 3. Chest x-ray (lateral view) with arrows showing margins of spread of contrast following injection of contrast medium through the catheter. Counter-clockwise rotation of the patient (i.e., note sternum) makes contrast appear more posterior anatomically. Subpleural location is indicated as spread of contrast appears to be posterior to vertebral body chain.

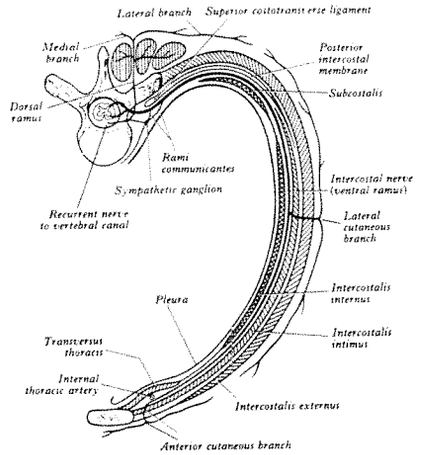

Figure 4. A diagram of the course of a typical intercostal nerve. Note that medial to the angle of the rib posteriorly the intercostal nerve lies between the pleura and the posterior (internal) intercostal membrane, i.e., the subpleural space (12). The subcostalis and intercostalis intimus muscle are not present. Note the angle that the pleura makes with the overlying skin surface medial to the posterior rib angle. Also note the communication of the subpleural space with the paravertebral space. (Reproduced with permission from Gray's *Anatomy*, British edition, Edinburgh: Churchill-Livingstone, Vol. 36, 1980.)

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this point (Fig. 4). On loss of resistance, the position of the advancing needle tip, in that circumstance, was in the intercostal space. Catheter placement medially with the needle in this position allows the catheter to communicate with the subpleural-paravertebral space. This is the case because, in the upper thoracic intercostal spaces near the posterior midline, the intercostal nerves run through the subpleural space, which is anatomically connected with the paravertebral space (12) (Fig. 4). Catheter localization in the subpleural-paravertebral space, with continuous administration of local anesthetic, provides unilateral, multisegmental analgesia without, in this case, development of tachyphylaxis. The analgesia using this technique may compare favorably with that seen with intrapleural or continuous intercostal block, but this requires further study.

We believe this method to be of value in treating the acute phase of thoracic HZ, and may have applications for other painful conditions. This technique represents a novel approach to the subpleural-paravertebral space, and was not difficult to perform in this patient. Further studies are required to assess efficacy in larger patient trials.

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Sixty Years Ago In

Anesthesia & Analgesia

C. Koller: Personal reminiscences of the first use of cocain (sic) as a local anesthetic in eye surgery: Current Researches in Anesthesia & Analgesia 1928;7:9–11.

This 1928 account by Koller, who at that time was living in New York City, of how he came to introduce cocaine as the first local anesthetic, is delightfully intimate and detailed, more informal and perhaps more revealing than are similar accounts that were subsequently published. The occasion for the 1928 reminiscence was his being honored for "meritorious research in anesthesia and analgesia" by the International Anesthesia Research Society and the Associated Anesthetists of the United States and Canada. In his presentation Koller clearly demonstrates that neither accident nor serendipity were involved in his important discovery. Instead, what Koller did was deliberate and carefully planned out in advance.

As Koller tells it, in the early 1880s he was a house surgeon on the staff of the Allgemeine Krankhaus in Vienna. He was also involved in experimental research of the eye in animals. For this, he needed anesthesia. "General narcotics," he found, however, to be totally unsuitable because of postoperative delirium and retching that endangered the operated eye. He tried chloral and other anesthetics without success and eventually had to discontinue his research. At about this time, his friends Drs. Sigmund Freud and Joseph Breuer, started using cocaine to treat a young physiologist who had become addicted to morphine because of a painful neuroma in the stump of an amputated thumb. They ran into problems, however, and in 1884 Freud asked Koller to join him in studying the physiologic systemic effects of cocaine. Using themselves as subjects, Freud and Koller took cocaine internally by mouth and, after a suitable wait for absorption to take place, measured their muscular strength and fatigue. In these experiments they confirmed the fact, previously recorded by Niemann in 1860, that when taken by mouth cocaine causes numbness of the tongue and lips. On this basis, Koller instilled a few drops of a cocaine solution in the eye of a frog, and later in that of a guinea pig. He found the cornea and conjunctiva to be anesthetized. He repeated these experiments on himself, on colleagues, and on patients. With minimal delay he brought the results of his experiments to the attention of ophthalmologists, the celerity of publicizing his observation being that, as he said, he "aspired to one of the much coveted positions of assistant to one of the large eye clinics." Thus, he had an associate, Dr. Brettauer of Trieste, read for him a preliminary report of his observations to a meeting of the German Ophthalmological Society of Heidelberg on September 15, 1884. In October Koller himself read a more elaborate paper before the Gesellschaft der Aerzte of Vienna. Subsequent publication of this paper in the *Wiener Medizinische Wochenschrift* and of translations in the *London Lancet* and the *New York Medical Record* called the attention of the world to this remarkable contribution. At about the same time, Koller also had an otolaryngologic friend evaluate and demonstrate the efficacy of topical cocaine for surgery in the mouth and throat. Koller also notes that to the best of his knowledge, the first person to make use of the local anesthetic action of cocaine by hypodermic injection was the Surgeon Professor Anton Woelfer, first assistant to the giant among 19th century surgeons, Theodore Billroth of Vienna. Regional anesthesia with cocaine was not just something for ophthalmologists. It was a discovery that affected the totality of surgery.

Diphenhydramine Reversal of Vancomycin-Induced Hypotension

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Key Words: COMPLICATIONS—bronchospasm, hypotension. ANTIBIOTICS, VANCOMYCIN—adverse reactions. ALLERGY—vancomycin.

The package insert for Vancocin HCl (vancomycin hydrochloride, Eli Lilly and Company) states, "There have been reports that the frequency of infusion-related events (including hypotension, flushing, erythema, urticaria, and pruritis) increases with the concomitant administration of anesthetic agents." The suggestion is then made that such events may be minimized by giving vancomycin as a 60-minute intravenous infusion before anesthetic induction.

Neurosurgeons at this medical center perform over 100 ventriculoperitoneal (VP) shunts and shunt revisions a year and want these patients to be given vancomycin at the time of operation. Because of the recommended 1 hour infusion time, it has been impractical to infuse the drug immediately before surgery. Therefore it has been given over 60 minutes after establishment of anesthesia in 84 consecutive cases without incident, until the patient herein described.

Case Report

A 2-year-old, 10-kg boy with a brain tumor was scheduled for emergency VP shunt because of impending brain stem herniation. After an intravenous thiopental induction, the trachea was intubated after paralysis with 1 mg vecuronium. Anesthesia was maintained with N_2O–O_2–isoflurane and peak inspiratory pressure (PIP) during controlled ventilation was between 12 and 15 cm H_2O. Systolic blood pressure (BP) was 80–90 mm Hg and O_2 saturation by pulse oximetry was 98%. Intravenous vancomycin infusion, 400 mg in 40 ml, was then started at a rate calculated to take 60 minutes to complete. Once a minute, the child was being given 0.67 ml containing 6.7 mg vancomycin. About 45 minutes later, slight movement of the patient prompted administration of a supplemental 0.25-mg dose of vecuronium through an injection port of the tubing carrying the vancomycin. The anesthesiologist then expedited delivery of the relaxant by flushing the tubing between injection port and vein with 5 ml of saline, injected within 10 seconds. About 3 minutes later, PIP increased as BP and O_2 saturation decreased, quickly reaching values of 45 cm H_2O, 50 mm Hg systolic, and 85%, respectively. Tidal volume decreased from 100 ml to 20 ml as the uncuffed endotracheal tube allowed the majority of delivered inspiratory volume to backflow into the oropharynx. The small ventilatory volume and this large leak prevented auscultatory assessment of breath sounds. Skin flushing could not be determined in this heavily pigmented patient. Metaproterenol aerosol added into the breathing circuit caused PIP to decrease modestly to 40 cm H_2O. Diphenhydramine, 12.5 mg IV, was then given, followed by prompt improvement in PIP, BP, and O_2 saturation, all returning to normal within 3 minutes. The remainder of the case was uneventful.

Discussion

Because bronchospasm and hypotension followed administration of vecuronium, the uncritical observer might conclude that the relaxant caused these sequelae. This conclusion is untenable in light of the lack of any untoward reaction by this patient to a prior, larger dose of vecuronium. The cause was clearly the rapid rate of vancomycin infusion that resulted from flushing the intravenous tubing.

The metered delivery rate of vancomycin was set at 6.7 mg/min. The volume of the tubing between injection port and intravenous catheter hub was 2.5 ml. This 2.5 ml contained 25 mg of the antibiotic. When the line was flushed with 5 ml saline over 10 seconds, we assume that this 25-mg dose was given within 5 seconds, a dose rate of 300 mg/min. This

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represented a 45-fold increase in rate, for a few seconds. Because it was followed by saline containing no relaxant, it appears that the 25 mg dose delivered within 5 seconds was sufficient to prompt a reaction, which responded dramatically to a therapeutic dose of an antihistamine.

Miller and Tausk (1) reported extreme hypotension, but not bronchospasm, which developed in an anesthetized adult neurosurgical patient given vancomycin at an unspecified rate. When the mean arterial pressure decreased to 30 mm Hg, the sitting patient was placed supine, her G suit was inflated and the intravenous fluid infusion rate was increased, which incidentally increased the vancomycin dose rate. When she then developed a skin rash, diphenhydramine, dexamethasone, and epinephrine were given and the blood pressure returned to normal. At this time (1977) the importance of infusion rate of vancomycin was not yet appreciated. It was two years later that Newfield and Roizen stressed the need to give this drug slowly and recommended infusion times of 30 minutes (2).

A 1981 article described a patient anesthetized for elective oral surgery who had been given 500 mg vancomycin over a 30-minute period when he suddenly became hypotensive (3). The authors of that report cautioned that the drug should be infused over 1 hour, and discussed direct depression of myocardial contractility by vancomycin as a likely cause of dose-related hypotension. They treated their patient by discontinuing vancomycin and administering methoxamine, $CaCl_2$ and O_2.

Two more reports were published in January/1984. Dajee et al. (4) described a patient given 500 mg vancomycin within 1 minute after he had been weaned from cardiopulmonary bypass during coronary artery bypass grafting. The blood pressure decreased precipitously and the heart arrested. Resuscitation drugs included $CaCl_2$, ephedrine and intracardiac epinephrine. The authors concluded that vancomycin "is a safe drug if administered cautiously as a 0.5% solution over 30–60 minutes." Odio et al. (5) reported results of a double-blind, prospective comparison of placebo to vancomycin, 15 mg/kg given as a 60 minute infusion one hour before cerebrospinal fluid (CSF) shunt procedures in children. Of 20 patients given vancomycin, seven (35%) had skin rashes that responded to antihistamines. One patient, an infant, had intraoperative hypotension "50 minutes into the vancomycin infusion", an apparent exception to their routine of giving the drug preoperatively. The authors mentioned previous reports of reactions to vancomycin during anesthesia and speculated that their case might have been another instance of this.

Our experience provides two points of particular interest. First, flushing the infusion tubing produced a brief pulse of drug delivery that evidently exceeded the safe limit. This suggests that rate, rather than total dose, is critical in producing untoward effects. Second, the reaction that followed was immediately reversed by the antihistamine diphenhydramine. The abrupt BP decrease from 80 to 50 mm Hg and the fact that it remained at the lower level until the antihistamine immediately restored it to 80 are consistent with a histamine-mediated toxic effect. Direct myocardial depression by vancomycin would not respond in this way. Evidence for vancomycin-related histamine release was reported recently by Levy et al. (6). The restoration of BP by diphenhydramine, the only resuscitative drug given to our patient, strongly supports their conclusion that histamine release is the cause of vancomycin-induced hypotension. There is no reason to believe that anesthesia per se favors such release. In fact, there is evidence that halothane inhibits histamine release (7). The idea that vancomycin infusion-related complications are more frequent during anesthesia is based only on anecdotal reports, not on a controlled study. If there *is*, in fact, a higher frequency of reactions intraoperatively, it is more likely to reflect inattention to infusion rates than interaction with anesthetic drugs.

We conclude that intravenous tubing carrying vancomycin should not be flushed and that diphenhydramine should be immediately available when this antibiotic is given.

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Life-Threatening Effects of Intravascular Absorption of $PGF_{2\alpha}$ during Therapeutic Termination of Pregnancy

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Prostaglandins are being increasingly employed for modulation of labor patterns and for induction of labor after fetal death (1). Prostaglandin E and F are administered intravenously or, in much larger doses, by intra-amniotic injection under ultrasonic guidance. Although this is frequently done without maternal monitoring, anesthesiologists may be called upon to provide analgesia during labor or monitored anesthesia care during the prostaglandin infusion. Although generally safe, intra-amniotic infusion may be complicated by intravascular injection or absorption of significant quantities of prostaglandin with life-threatening hemodynamic consequences (2,3). Hemodynamic effects of intravascular injections of prostaglandins are usually short-lived, due to short plasma half-life, so treatment usually entails supportive measures for a period of only a few minutes (4). We report a case where intra-amniotic injection of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) resulted in alternating hypotension and severe hypertension associated with bronchospasm and severe peripheral vasoconstriction, which lasted nearly 2 hours.

Case Report

The patient, a healthy, 29-year-old primagravida with no previous medical problems, was admitted for induction of labor with a diagnosis of oligohydramnios and late second trimester fetal demise. She had no known allergies, and no history of asthma or hypertension. The patient was anxious, and requested epidural analgesia for the amniocentesis and labor, which was expected to last only a few hours. An epidural catheter was placed at the L2-3 interspace without difficulty, and, after a test dose of 3 ml of 1.5% lidocaine with 15 μg epinephrine, 6 ml of 0.25% bupivacaine injected through the catheter produced a sensory level to the eighth thoracic dermatome. Blood pressure remained stable, at approximately 120/70 mm Hg. The patient's continued anxiety about the procedure led to administration of 7.5 mg of midazolam and 5 mg of morphine sulphate, in increments, over the next hour during the amniocentesis under ultrasonic guidance. Because of the severe oligohydramnios, an amniodistention procedure was performed: 300 ml of Ringer's lactate solution were infused into the uterine cavity as a diluent for the prostaglandin solution which was to be injected. A test injection into the uterine cavity of 1 mg $PGF_{2\alpha}$ was then made. After this, 80 g urea and 20 mg $PGF_{2\alpha}$ were injected through the same intra-amniotic catheter over 10 minutes. A few minutes after the infusion, with the onset of uterine contractions, the patient suddenly complained of burning in her face and chest accompanied by difficulty breathing. Oxygen was administered by face mask. The sensory level of the epidural was rechecked and found to be at T-9. Over the next few minutes, the patient became hypotensive with a systolic blood pressure reading of 70 mm Hg by cuff. Peripheral pulses could not be palpated, although she remained alert and oriented. She was treated with 35 mg ephedrine, in increments, and the IV infusion of fluids was increased. She continued to be dyspneic even while sitting, although her skin color was pink. Over the next 5 minutes, the patient's extremities became mottled, and she complained of chest pressure, severe headache and extreme tenderness of her breasts. Blood pressure rose to 220/135 mm Hg. Heart rate was 95 beats/min and respiratory rate was 44 breaths/min. At this time, oxygen saturation by pulse oximetry was 94% and expiratory wheezing developed. The patient was treated with 50 mg labetalol given over 15 minutes reducing her blood pressure to 134/77 mm Hg but producing no symptomatic relief. She also received nebulized bronchodilator therapy. Peripheral pulses still could not be felt. Over the next two hours,

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until delivery of the fetus, her blood pressure was extremely labile with sudden swings over a range of 76/50–225/125 mm Hg. Her skin remained mottled and cold and the headache and dyspnea continued. Multiple attempts at placement of an arterial line in the radial, brachial, dorsalis pedis, and posterior tibial arteries were unsuccessful, presumably due to the extreme peripheral vasoconstriction. The patient could not lie down sufficiently to allow femoral artery puncture. During this time, an external jugular central venous catheter placed with the patient sitting, showed central venous pressure to be 13 cm H_2O. A venous blood gas, approximately 20 minutes after the initial event showed pH 7.33, Po_2 36 mm Hg, Pco_2 41 mm Hg, base excess (BE) −4 mEq/L, and HCO_3^- 21 mEq/L. Plasma electrolyte levels were within normal limits. An arterial blood sample, finally obtained 1 hour later showed pH 7.43, Po_2 174 mm Hg, Pco_2 28 mm Hg, BE −4 mEq/L, HCO_3^- 28 mEq/L, while breathing 6 l/min O_2 by mask. Chest x-ray and ECG were both normal.

The patient had painful contractions throughout the approximately 2 hours after injection of the prostaglandin. At that time labor had progressed sufficiently to allow artificial rupture of the amniotic membranes in an attempt to remove any remaining prostaglandin. With this, her blood pressure stabilized. Five milliliters 2% lidocaine were injected through the epidural catheter to provide analgesia for delivery, which proceeded without further incident.

Discussion

Dinaprost trimethamine (prostaglandin $F_{2\alpha}$-THAM), used in this patient, was originally marketed for induction of labor but is currently unavailable from the manufacturer. Its biological effects are similar to other products available for a wide variety of indications in obstetrics. $PGF_{2\alpha}$ acts by stimulating contraction of smooth muscle in the uterus. Concomitant effects on smooth muscle elsewhere, including the gastrointestinal tract, bronchial smooth muscle, and arteriolar smooth muscle, are responsible for its side-effects. Most $PGF_{2\alpha}$ is removed in a single pass through the lungs. Plasma half-life is less than one minute, but half-life in the amniotic fluid is 3–6 hours (4). Uterine hypertonicity and rupture have been reported after $PGF_{2\alpha}$ administration (5). Vasomotor and vasovagal effects include bradycardia, hypotension, syncope, and hypertension (6); flushing and dysrhythmias have been described (6,7) as well as severe bronchoconstriction and feelings of chest constriction, especially in patients with a history of asthma (8). Cardiopulmonary arrest and death due to $PGF_{2\alpha}$ have been reported (2,3).

Secher et al. investigated the cardiopulmonary effect of low doses of prostaglandin $F_{2\alpha}$ in five anesthetized patients (6). When 100–300 μg/min of prostaglandin $F_{2\alpha}$ were infused intravenously, a 40% increase in cardiac output was seen, together with a 25% increase in systemic pressure and a 125% increase in pulmonary artery pressure. Calculated systemic vascular resistance thus decreased slightly and pulmonary vascular resistance increased markedly. Two of five patients developed ventricular bigeminy. Material oxygenation also decreased, presumably due to increased ventilation–perfusion mismatch. The predominantly pulmonary effect observed by Secher et al. might be expected because most $PGF_{2\alpha}$ is removed by one pass through the lungs (4). However, it may not be possible to extrapolate their findings to patients who receive in intravascular injections of an order of magnitude more $PGF_{2\alpha}$. Although bronchoconstriction was clearly part of the clinical picture for our patient, she was initially hypotensive and then had a systolic blood pressure almost twice that recorded before injection of prostaglandin. Her marked peripheral vasoconstriction must also have been associated with an increased systemic vascular resistance.

Our initial differential diagnosis for the patient in this report included amniotic fluid embolism, uterine rupture, and intravascular absorption of prostaglandin $F_{2\alpha}$. A high level of epidural anesthesia was eliminated from the differential because of the timing, the level of pinprick anesthesia, and the patient's ability to feel uterine contractions. The lack of peripheral pulses was at first ascribed to her initial hypotension. Difficulty with peripheral access resulting from the extreme vasoconstriction made evaluation of acid–base status and arterial oxygenation difficult.

In light of the patient's subsequent hypertension, prostaglandin absorption is the most likely etiology for her clinical course. Most remarkable was the extreme degree of peripheral vasoconstriction. Pulse oximetry provided reassuring evidence that the patient was not hypoxemic. Interestingly, although oxygen saturation could be measured when the probe was placed on the patient's ear lobe, no signal could be obtained from the patient's toes or fingers. Additionally, it was extremely difficult to measure blood pressure by auscultation despite attempts by experienced nurses and physicians. Two automated blood pressure cuffs (Dinamap and Hewlett Packard) were able to provide blood pressure readings throughout the period of extreme peripheral vasoconstriction while attempts at arterial cannulation were unsuc-

cessful. We were reluctant to begin a nitroprusside infusion in the absence of arterial pressure monitoring, but this might have provided greater control of the rapidly fluctuating blood pressure than the labetolol, which was initially given, and might have improved peripheral perfusion to the extent that an arterial line could have been placed.

Given the short plasma half-life of $PGF_{2\alpha}$, we were surprised that the patient did not rapidly improve from what appeared to be an intravascular injection. In retrospect, we believe that the extreme lability of the patient's blood pressure resulted from repeated intravascular boluses of prostaglandin caused by the continuing uterine contractions.

What is the anesthesiologist's role in monitoring patients scheduled for prostaglandin induction of labor? In the case reported here, infusion of saline into the uterine cavity, difficulty in placing the intra-amniotic catheter, and possible disruption of the amniotic membranes after fetal death may all have contributed to the intravascular absorption of $PGF_{2\alpha}$. Each of these may be present when prostaglandins are used for termination of pregnancy. In light of the potentially fatal complications attending intravascular injection of $PGF_{2\alpha}$, we recommend monitored anesthesia care for inductions after fetal demise. In these cases, oligohydramnios may make placement of the intrauterine catheter more difficult than usual. Use of a test intrauterine injection of $PGF_{2\alpha}$, as recommended by the manufacturer, decreases the likelihood of intravascular absorption, but does not eliminate it, as in the situation described above, in which uterine contractions were apparently the cause of repeated intravascular uptake.

When prostaglandins are infused, the anesthesiologist must be prepared to deal with intravascular collapse, hypertension, and refractory bronchospasm. The anesthesiologist should have immediate access to pulse oximetry and automated blood pressure measurement. Supportive treatment with oxygen and bronchodilators is obviously indicated as are efforts to remove the remaining prostaglandin from the uterine cavity. Use of arterial vasodilators is indicated during the periods of extreme hypertension.

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Use of Esmolol in the Intraoperative Management of Pheochromocytoma

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Key Words: SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—esmolol. SURGERY—pheochromocytoma.

The intraoperative management of the hyperadrenergic state associated with pheochromocytoma presents a formidible anesthetic challenge. The development of new and effective pharmacotherapy has allowed better control of the hemodynamic changes that can occur during this type of surgery. We report a case in which the short-acting β-blocker esmolol was of benefit in perioperative management of pheochromocytoma. To our knowledge this represents the first reported use of this agent in this condition.

Case Report

A 35-year-old woman presented with a right adrenal pheochromocytoma. Eleven years earlier, during her second pregnancy, she was first found to be hypertensive and hyperglycemic. The initial diagnosis of toxemia of pregnancy was reevaluated when her hypertension persisted after delivery. In the 10 years before admission, the patient had frequent headaches accompanied by blurred vision, nausea, palpitations, diaphoresis, paresthesias, and shortness of breath. Her hypertension was treated with a variety of medications including diuretics, β-adrenergic blockers, and central antihypertensives. Between 1982 and 1987 she was admitted three times to intensive care units for chest pain but did not suffer a myocardial infarction. Over the same period she developed shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, and worsening exercise tolerance. She had a history of hypertensive reactions to meperidine and atropine.

In February of 1987 the patient underwent a first rib resection and scalenectomy under general anesthesia for presumed thoracic outlet syndrome. On emergence her blood pressure increased to 240/170 mm Hg. Investigation into the cause of the patient's hypertension was initiated. A 24-hour urine collection revealed a markedly elevated level of norepinephrine (419 μg/24 hours; normal < 100), mild elevation of vanillylmandelic acid (19.6 mg/24 hours; normal 2–7), and normal levels of epinephrine (8 μg/24 hours; normal < 15) and dopamine (110 μg/24 hours; normal 65–400). Computerized tomography of the abdomen demonstrated a right adrenal mass. The patient was referred to our institution for resection of a presumed norepinephrine-secreting pheochromocytoma.

The patient was given oral phenoxybenzamine 10 mg twice per day before admission but was not compliant. Other outpatient medications included nadolol 20 mg per day, hydrochlorothiazide 25 mg per day, ranitidine 150 mg per day, and diazepam 2 mg per day. Review of systems was remarkable only for a symptomatic hiatal hernia. Admission blood pressure was 170/100 mm Hg with a pulse of 100 beats/min. Weight was 63 kg. There was no evidence of congestive heart failure. The admission ECG was notable for T-wave inversions in leads III, AVF, and V_{1-3}.

After premedication with oral diazepam 10 mg and ranitidine 150 mg intravenously, the patient was brought to the operating room. A percutaneous radial arterial line was placed, revealing an initial blood pressure of 170/110 mm Hg, with a pulse of 80 beats/min. Central venous and pulmonary artery catheters were inserted percutaneously via the right internal jugular vein. Fentanyl 250 μg and midazolam 8 mg were slowly administered intravenously during catheter placement. Phentolamine 10 mg was given by slow IV infusion. Mean blood pressure (MBP) responded by decreasing to 105 mm Hg while pulse rate transiently increased to 120 beats/min. Complete hemodynamic data are presented in Table 1. Values

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Table 1. Hemodynamic Data Before and During Surgery

Time	MBP (mm Hg)	HR (beats/min)	RAP (mm Hg)	$\overline{PAP}$ (mm Hg)	PCW (mm Hg)	CI ($L \cdot min^{-1} \cdot m^{-2}$)	SVR ($dynes \cdot sec \cdot cm^{-5}$)
Before induction	82	86	12	34	12	3.5	982
Immediately after induction*	75	91	16	18	11	3.8	773
Before tumor manipulation†	79	83	12	15	12	2.8	1164
Tumor manipulation‡	115	85	15	23	13	2.0	2581
After tumor removal§	81	85	9	18	10	3.3	1088

Abbreviations: MBP, mean blood pressure; HR, heart rate; RAP, right atrial pressure; $\overline{PAP}$, mean pulmonary artery pressure; PCW, pulmonary capillary wedge pressure; CI, cardiac index; SVR, systemic vascular resistance.

*Drugs: esmolol 0.1 mg/kg/min, enflurane 1%.

†Drugs: nitroprusside 0.13 μg/kg/min, esmolol 0.2 mg/kg/min, enflurane 1%.

‡Drugs: nitroprusside 3.3 μg/kg/min, esmolol 0.3 mg/kg/min, enflurane 1%.

§Drugs: enflurane 0.5%.

before the induction of anesthesia were compatible with a mild hyperdynamic state. Esmolol 0.5 mg/kg was infused over 1 minute followed by a constant infusion of 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Mean blood pressure decreased slightly while pulse decreased to 85 beats/min. The low systemic vascular resistance (982 $dynes \cdot sec \cdot cm^{-5}$) reflects the α-adrenergic blockade by phentolamine.

Anesthesia was induced using fentanyl 10 μg/kg, pancuronium 0.1 mg/kg, lidocaine 1 mg/kg, and thiopental 100 mg. The patient was mask-ventilated with enflurane in 100% oxygen until muscle relaxation was adequate to permit laryngoscopy and tracheal intubation. Mean blood pressure decreased to 75 mm Hg. In view of the patient's history of hiatal hernia, cricoid pressure was applied throughout the induction to minimize gastric air entrainment and to prevent aspiration. The trachea was intubated easily without change in MBP. Hemodynamic data immediately after intubation (Table 1) included a decrease in systemic vascular resistance (SVR) associated with a mild increase in heart rate and cardiac index (CI).

Anesthesia was maintained with enflurane 0.5–1% in oxygen 100%. Muscle relaxation was maintained with pancuronium. Nitroprusside 0.13–3.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was used to maintain MBP in the range of 80–110 mm Hg. Heart rate remained between 80 and 90 beats/min. Propranolol 3 mg IV was given and esmolol was given in incremental amounts up to 0.3 $mg \cdot kg^{-1} \cdot min^{-1}$. A reduction in blood pressure and cardiac index was achieved with esmolol, allowing for a decrease in the dose of nitroprusside.

Operative manipulation of the tumor resulted in bradycardia and hypertension (heart rate 42, MBP 165 mm Hg). This was easily controlled by changing the rates of infusion of nitroprusside and esmolol. The tumor was 8 cm in diameter and lay behind the vena cava. Both renal veins and the inferior vena cava were compressed and splayed over the tumor mass. It was necessary to dissect tumor away from these vessels to expose and ligate the right adrenal vein. Ligation of this vein and removal of the tumor resulted in a decrease in mean arterial blood pressure and heart rate. This permitted discontinuation of both nitroprusside and esmolol. Five units of packed red blood cells and 8500 ml Ringer's lactate solution were given intraoperatively. Estimated blood loss was 2400 ml. The patient was taken to the intensive care unit while still intubated. Mean blood pressure and heart rate on arrival were 80 mm Hg and 85 beats/min, respectively. She was gradually weaned from the ventilator and extubated, and made an uneventful recovery.

Discussion

Before the advent of pre- and perioperative control of the hyperadrenergic state associated with pheochromocytoma, mortality was as high as 45% (1). Use of drugs to effectively control hypertension has been associated with a reduction in mortality to 3% or less (2–4), even when these agents were not instituted before operation (5). With the use of these agents came the recognition of the importance of blood volume contraction in the untreated state. Correction of hypovolemia has also been of importance in the reduction of mortality (6). Most experts now recommend the use of preoperative α-blockade with phenoxybenzamine, accompanied with gentle volume expansion (7,8).

The need for pre- and perioperative β-blockade is less universally accepted. If tachycardia, arrhythmias (most often premature ventricular contractions), or myocardial ischemia are present despite adequate α-blockade, most authors recommend the use of β-blockers (2,3,5–11). Some authors routinely use β-blockade (4). There are several potential objections to routine use of β-blockers. These include hypertension in the incompletely α-blocked patient (2,3,5,6,8–11), congestive heart failure and pulmonary edema in the patient with compromised cardiac function (3,8,12), precipitation of bronchospasm (3,8,12), and second or third degree heart block (8).

Pancuronium is known to produce muscarinic blockade and might, therefore, cause tachycardia and blood pressure elevation. In this case, pancuronium was used only after establishing β-adrenergic blockade and only in the setting of an adequate level of anesthesia, particularly during laryngoscopy, periods of high surgical stress, and tumor manipulation.

We chose to provide a background of β-blockade by using a moderate dose of propranolol immediately after induction. This was given only after calculating a low systemic vascular resistance from the first two hemodynamic profiles obtained (Table 1), evidence that the phentolamine given previously had blocked a significant proportion of α-receptors. This baseline level of β-blockade was considered to be a safe alternative in the setting of a long, difficult dissection of a large tumor. It also prevented β-blockade withdrawal postoperatively, which could result in coronary ischemia.

Use of esmolol allows for the intraoperative management of those complications associated with excessive β-stimulation. Hypertension, which may in part result from β-stimulated myocardial contractility, may also be reduced by esmolol. The drug has been used in conjunction with a number of anesthetic regimens to attenuate the hyperdynamic response to intubation (13,14). It has been reported to effectively attenuate the tachycardia and hypertension associated with the use of ketamine as an induction agent (15), a situation resulting in catecholamine excess not unlike that observed in pheochromocytoma. Esmolol has been particularly useful in coronary artery bypass graft surgery, allowing for control of heart rate without ischemia or myocardial failure throughout this procedure (16–18). Its short duration of action and rapid reversibility allows the anesthesiologist to overcome most of the objections raised by opponents of beta blockade. Onset is rapid, within two minutes in most cases (19). Elimination occurs in nine minutes in healthy volunteers (20) and is largely reversed in thirty minutes in all cases (19,21). Finally, of particular interest in the management of pheochromocytoma, esmolol is associated with a rapid decrease in systolic blood pressure without effect on diastolic pressure (22,23). In the case presented here this aspect of esmolol activity may have been particularly helpful as myocardial perfusion was probably better maintained.

In this case, the hemodynamic control achieved is demonstrated by the data presented in Table 1. There was a brief period of hypertension and decrease in cardiac index (2.0 $L \cdot min^{-1} \cdot m^{-2}$) associated with a rise in systemic vascular resistance (2581 $dynes \cdot sec \cdot cm^{-5}$), which occurred during manipulation of the tumor. While β-blockers might be expected to depress myocardial contractility and cardiac index further in the face of a markedly elevated afterload, the use of a short-acting agent with rapid reversibility on discontinuation can minimize the duration of myocardial depression, should it occur.

We conclude, therefore, that esmolol has significant potential for the treatment of cardiovascular abnormalities associated with excess β-stimulation of the patient undergoing resection of pheochromocytoma.

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Patient-Controlled Anxiolysis with Midazolam

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Key Words: HYPNOTICS, BENZODIAZEPINES—midazolam. CRITICAL CARE, INTENSIVE CARE UNIT—anxiety.

Care of critically ill patients has been centered in specialized units in which the environment is more often determined by the physical needs of sophisticated machines rather than out of concern for patients' psychological wellbeing (1). The incidence of fear and anxiety has been reported to be as high as 70% (2). Patients frequently report feelings of loss of control, fear of physical harm, and a sense of impending doom (3).

Benzodiazepines have been the mainstay of pharmacologic intervention to provide anxiolysis in the intensive care unit (ICU) (4,5). But, as with analgesics, anxiolytics administered intermittently on an "as needed" or "prn" basis may not provide consistent or continuous relief. Midazolam has been administered as a continuous infusion, but this has the inherent risk of undue sedation (6). Applying the principles and equipment of patient-controlled analgesia (PCA) to the administration of midazolam, we developed a protocol for providing anxiety management to patients in the ICU. We present two cases to illustrate what we have termed patient-controlled anxiolysis (PCAx).

Case Reports

Two adult patients who experienced anxiety in the ICU are discussed. Following institutional approval, informed written consent was obtained the institution of PCAx. A patient-controlled pump (Lifecare PCA Infuser, Abbott Laboratories, Chicago, IL) was used to deliver midazolam in a solution of 0.25 mg/ml. The device was set to administer 1 ml when triggered by the patient. An internal lock-out mechanism limited the triggering activation to once every 8 minutes, with a rolling total administration set at 5 mg per any 4-hour period. To assess the efficacy of self-administered midazolam, the patients rated their anxiety daily on a 0 to 10 scale, 0 being "no anxiety" and ten being "extreme anxiety". Physicians and nurses taking care of the patients similarly evaluated the patients' affect.

Case 1.

A 65-year-old woman with a history of Takayasu's disease presented with acute mesenteric ischemia. Revascularization of the superior mesenteric artery was performed using an aortic graft, resection of the terminal ileum and an ileostomy. Because recovery was complicated by poor pulmonary function, she remained intubated in the ICU. By the fourth postoperative day she clearly communicated the distress caused by her continued intubation and her fear of the ICU environment. The patient was offered midazolam, which she self-administered at 2 to 4 mg/day over the next 13 days. With extubation on the 17th postoperative day, she ceased using the midazolam. The patient rated her initial anxiety at "8," but was able to decrease it to a "1" during the self-administration of midazolam.

Case 2.

A 29-year-old woman underwent a partial nephrectomy to remove a renal cell carcinoma. The postoperative course was complicated by adult respiratory distress syndrome that necessitated ventilatory support. During the third week of intubation she became extremely distressed and anxious. Midazolam therapy was instituted, with an average self-administration of 4 to 8 mg/day over the next 18 days. After extubation the patient decreased her use of midazolam to 1 to 3 mg/day, and stopped using the midazolam 3 days later. Before treatment she had rated her initial anxiety at a "10." She was able to reduce it to a "2" with self-administered midazolam.

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Table 1. With the institution of PCA, there is a reduction in both the anxiety score and analgesic requirement

	Before	After
Anxiety score		
Case 1	8	1
Case 2	10	2
IV morphine, mg/day		
Case 1	10–12	0–2
Case 2	16–20	2–4

Discussion

Our goal was to promote a sense of wellbeing in selected ICU patients by giving them an element of control over the pharmacologic management of anxiety. Enthusiastic patient acceptance of patient-controlled analgesia for postoperative pain led us to modify the technique to provide anxiolysis. Use of the PCA pump allows small amounts of anxiolytics to be given intravenously at frequent intervals. This produces adequate relief of anxiety without excessive sedation. ECG, respirations, and oxygen saturation by pulse oximetry were monitored continuously in both patients. The incremental doses did not significantly alter blood pressure or heart rate. Neither of the patients developed respiratory depression or oversedation. Usage correlated with major events such as invasive procedures and provided the additional benefit of amnesia for these stressful events. By self-report, as well as nursing and physician evaluation, the patients were able to substantially decrease their anxiety (Table 1).

Midazolam is the benzodiazepene of choice because it has a rapid onset, a short elimination half-life of 1.5 to 3.5 hours, and is void of significant pharmacologically active metabolites (7). With therapeutic doses there is minimal respiratory or cardiovascular depression (8). Of note, in both our patients analgesic requirements decreased. Benzodiazepines have been reported to influence the release of enkephalins in several brain regions related to pain processing (9,10).

In conclusion, we found the use of a patient-controlled device for the self-administration of midazolam to be a promising means of controlling the stress and anxiety associated with the ICU environment. Reasonable starting parameters are an incremental dose of 0.25 mg midazolam and a lockout interval of 10 minutes. Until further experience is obtained, this technique should be restricted to the ICU for use with ventilated patients and to those whose respirations are monitored. Patients who are mentally alert and able to comply with instructions are suitable candidates for patient-controlled anxiolysis.

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Management of One-Lung Anesthesia in an Anticoagulated Patient

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Key Words: ANESTHESIA, THORACIC—one-lung. BLOOD, ANTICOAGULANTS—chest surgery.

Intrabronchial bleeding and bronchopleural fistula are absolute indications for isolation of an affected lung during thoracotomy (1). We recently anesthetized a patient with the anticardiolipin syndrome and associated hypercoagulable state who required full anticoagulation therapy for treatment of acute pulmonary embolism. Emergency thoracotomy was performed for multiple episodes of hemoptysis, hemorrhagic pleural effusion, and suspected bronchopleural fistula. The potential risk of airway trauma and bleeding associated with manipulation of a bulky double-lumen endobronchial tube in this patient prompted us to use a single-lumen endotracheal tube with a built-in, small diameter, movable bronchial blocker (Univent). (Fuji Systems Co., Ltd 1-11-1 Ebisu, Shibuya-Ku, Tokyo 150, Japan.)

Case Report

A 26-year-old woman was scheduled for emergency thoracotomy for multiple episodes of hemoptysis, hemorrhagic pleural effusion, and suspected bronchopleural fistula. The most recent episode of bleeding into her airway occurred approximately 10 hours earlier; she did not have hemoptysis at the time of surgery. She had the anticardiolipin syndrome with an associated hypercoagulable state. Five months earlier, right axillary and subclavian vein thrombosis and right middle lobe pulmonary embolus occurred. Her symptoms subsided after treatment with intravenous heparin followed by oral warfarin. However, after discharge from the hospital, she did not continue taking warfarin. She was readmitted 4 days before surgery and a pulmonary angiogram was performed because of dyspnea, fever, hemoptysis, and left sided pleuritic chest pain; it showed a large embolus in the left main pulmonary artery. Intravenous heparin (1,000 U/hr) was given but she continued to experience hemoptysis. The following day a large sanguineous left pleural effusion and consolidation of the underlying pulmonary parenchyma developed. A left thoracostomy tube was inserted 2 days after admission but emergency surgical exploration was planned 2 days later because drainage was inadequate. Heparin therapy was to be continued intraoperatively to prevent further thrombosis.

Preoperatively, a small, continuous air-leak from her chest tube was noted. Arterial pH was 7.39, $PaCO_2$ 39 mm Hg, and PaO_2 90 mm Hg while breathing room air. The partial thromboplastin time (PTT) was 66 seconds with a control of 29 seconds and the prothrombin time (PT) was 11.1 seconds with a control of 11.9 seconds. On arrival in the operating room she was in no respiratory distress. Two peripheral IV lines and a radial arterial catheter were placed. After preoxygenation, anesthesia was induced with fentanyl (100 μg) and thiopental (300 mg), and after succinylcholine (100 mg), direct laryngoscopy was performed with a Univent single-lumen endotracheal tube with a movable blocker (see later) inserted atraumatically into the trachea until its cuff was beyond the vocal cords. After ascertaining that breath sounds were bilaterally equal, the endobronchial blocker was released and advanced into the left mainstem bronchus, guided with a fiberoptic bronchoscope. Its cuff was inflated, and isolation of the lung was confirmed by auscultation. No airway bleeding occurred during this maneuver. The patient was placed in the right lateral decubitus position and a left thoracotomy was performed at a time when the right lung was being ventilated. Anesthesia was maintained with 100% O_2, fentanyl (400 μg), and isoflurane (1–1.5%), plus pancuronium (12 mg), during the 2½-hour procedure. Surgical exploration revealed hemorrhagic infarction of the left lower lobe

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and a bronchopleural fistula involving the left lower lobe. A left lower lobectomy was performed without complication. However, during chest closure, wound bleeding necessitated heparin neutralization with protamine 0.5 mg/kg. Intraoperative blood loss was 1100 ml and the patient was given three units of packed red blood cells. PaO_2 remained >300 mm Hg during one-lung ventilation. At the conclusion of surgery, the bronchial blocker of the Univent tube was withdrawn and the patient was brought to the recovery room while intubated. Ventilation was controlled using a tidal volume of 700 ml and a respiratory frequency of 12 breaths/min. She was weaned from the ventilator and extubated several hours later. Her hospital course proceeded uneventfully and she was discharged on oral warfarin therapy 10 days after surgery. She was free of further thrombosis 3 months postoperatively.

Discussion

In our patient, as in most cases of tracheobronchial hemorrhage, isolation of the affected lung and selective ventilation of the normal lung was a valuable complement to surgical treatment. The bleeding lung may be isolated from the nonbleeding one by use of a double-lumen endobronchial tube, a single-lumen endotracheal tube, or an endobronchial blocker. Double-lumen tubes may be difficult to place and require significant manipulation. Mucosal damage and bleeding may occur with their placement. Numerous reports have emphasized the potential for tracheobronchial trauma, including rupture, by modern double-lumen endobronchial tubes (2–6). Advancement of a single-lumen tube endobronchially can isolate and permit ventilation of only the left lung if the distance between the carina and the upper lobe bronchus take-off matches the length of the tube cuff. This technique cannot be used for left lung lesions that require introduction of the tube into the right main stem bronchus, because the distance from carina to right upper lobe bronchus is frequently shorter than the length of the tube cuff. In our patient, whose anticoagulation therapy could not be stopped, an endotracheal tube with a movable bronchial blocker (7) appeared to be the safest and most practical alternative.

Endobronchial blockers were developed over 40 years ago (8) but fell out of favor because of difficulty in placing them and frequent displacement, causing airway obstruction or spillage. Their use has largely been supplanted by modern double-lumen tubes. The Univent tube we used consists of an endotracheal tube with a small anterior channel that contains an endobronchial blocker (2-mm diameter) with a low pressure, high volume cuff (7,9,10) (Fig. 1). With the Univent tube, the blocker may be advanced as much as 8 cm beyond the tip of the main tube. After intubation the blocker is advanced into the desired bronchus, guided with a fiberoptic bronchoscope (7). One-lung ventilation is achieved by inflating the distal blocker cuff. The Univent tube is a technical improvement over conventional endobronchial blockers because the blocker is attached to the main tube and thus its displacement is less likely. The blocker also contains an axial lumen through which suctioning, O_2 insufflation, and jet ventilation may be accomplished. Two-lung ventilation can be restarted by deflating the bronchial cuff and withdrawing it into its housing in the endotracheal tube. This tube eliminates the need for replacing a double-lumen tube with a single-lumen endotracheal tube when prolonged ventilation is required. In a recent study of patients undergoing thoracotomy, the Univent tube was easier to insert than double-lumen tubes while being equally effective in establishing one-lung ventilation. In the same series, no patient experienced tracheal or mainstem bronchial injuries (11).

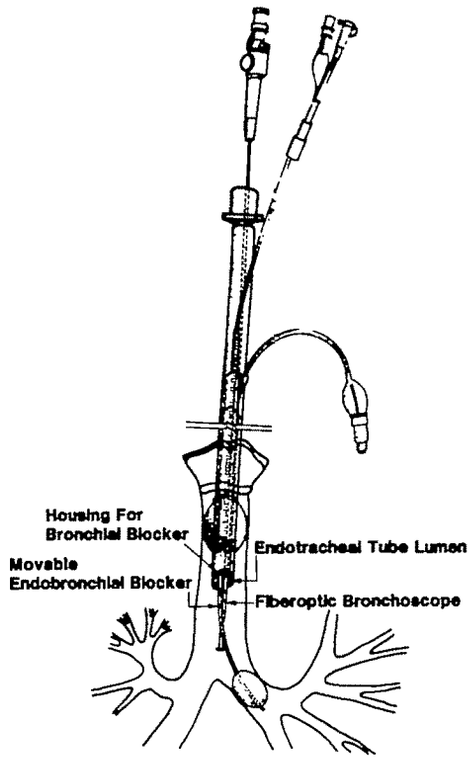

Figure 1. Schematic drawing of the Univent endotracheal tube with movable bronchial blocker.

In patients who are anticoagulated or have a bleeding diathesis, the typically atraumatic insertion of the

Univent tube, with its small diameter movable bronchial blocker, is a viable alternative to placement of a double-lumen endobronchial tube.

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Effect of Plasma Cholinesterase Activity on the Duration of Action of Succinylcholine in Patients with Genotypically Normal Enzyme

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Key Words: ENZYMES—plasma cholinesterase. NEUROMUSCULAR RELAXANTS—succinylcholine.

The brief duration of action of succinylcholine in humans is due to its rapid hydrolysis by plasma cholinesterase, an enzyme synthesized in the liver. Succinylcholine neuromuscular blockade may, therefore, be prolonged in patients with either a low level of plasma cholinesterase activity or a genotypically abnormal form of that enzyme (1–4). A number of factors have been identified as the cause of deficiencies of cholinesterase in humans, including chronic liver disease (5), pregnancy (6), acetylcholinesterase inhibitors (7), cancer (8), and some cytotoxic drugs (9). Despite these reports, it has generally been believed that, even in the presence of low cholinesterase activity, the increase in duration of apnea and return to 100% muscle twitch activity is rarely clinically relevant unless the surgical procedure is of short duration.

In the most complete study to date, Viby-Mogensen (10) concluded that the duration of action of succinylcholine correlated linearly with the inverse plasma cholinesterase activity. Other investigators have supported this view (11,12). However, these studies were completed either before the advent of monitors of neuromuscular function or the discovery of genotypically abnormal plasma cholinesterase forms or were performed in patients to whom volatile anesthetics were administered. Therefore no controlled study has yet been performed demonstrating the direct effect of genotypically normal plasma cholinesterase activity level on the duration of apnea and return to 100% twitch activity in the absence of drugs with known respiratory depressant effects or muscle relaxant properties.

Patients undergoing orthotopic liver transplantation for severe end-stage hepatic disease frequently have minimal or even no measurable plasma cholinesterase activity. This patient population, therefore, makes an ideal test group for correlating cholinesterase activity with the duration of action of succinylcholine because these patients usually have cholinesterase deficiencies of normal enzyme genotype (E^uE^u). The transplantation procedure takes several hours to complete, thus allowing sufficient time for the observation of the prolongation in duration of succinylcholine neuromuscular blockade.

Materials and Methods

Between March 1987 and September 1987, 26 consecutive patients with end-stage liver disease undergoing orthotopic liver transplantation were studied and served as the test group (group 1). The mean age of patients in group 1 was 41.6 years. Nineteen patients without liver disease undergoing surgical procedures unrelated to the liver or biliary tract during this same period served as controls (group 2) and had a mean age of 43.5 years. Both groups of patients were free from any disease affecting the neuromuscular junction and were taking no medication that might potentially affect the duration of neuromuscular blockade. This study was approved by the Mayo Clinic Institutional Review Board and informed consent was obtained on all patients.

After rejection of 5 patients in group 1 with either normal cholinesterase activity levels or abnormal dibucaine numbers, 21 patients were left in group 1 with low cholinesterase activity and normal dibucaine numbers (when calculations were possible); (Dibucaine numbers were unobtainable on patients with cholinesterase levels below 3 units/ml because of lack of precision of the assay at this level. Despite

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this, in patients with cholinesterase activity below 3 units/ml, the addition of dibucaine to serum samples resulted in the degree of cholinesterase inhibition expected in patients with normal genotypes of that enzyme). All patients in group 2 (n = 19) had normal cholinesterase activity and normal dibucaine numbers.

Before the induction of anesthesia, a venous sample was obtained for plasma cholinesterase activity level and dibucaine number. Cholinesterase levels were performed using the Du Pont automatic clinical analyzer (13). This is a colorometric assay measured at 600 nm using butyrylthiocholine as a substrate. Normal cholinesterase activity is between 8–18 international units per milliliter of serum with this assay. Dibucaine numbers were obtained with the same assay system by adding dibucaine to the venous sample and determining the amount of inhibition (14). Normal dibucaine inhibition is between 70–90% with this assay for patients with homozygous normal genotype (E^uE^u) and between 50–70% for heterozygotes (E^uE^a).

The results of the plasma cholinesterase level and dibucaine numbers were not available until after the testing procedure was completed. No patient in our study had a plasma cholinesterase activity level above the normal range of 18 IU/ml. All patients on whom dibucaine numbers were obtainable had greater than 84% dibucaine inhibition, which was clearly within the range indicative of normal homozygous (E^uE^u) cholinesterase enzyme.

No premedication was given to either group of patients. All patients had their nondominant upper extremity placed in an apparatus designed to detect maximum thumb adduction displacement with ulnar nerve stimulation at the wrist with the use of a force displacement transducer (15). A series of four supramaximal (2 Hz) single stimuli was applied to the nerve (train-of-four) every 12 seconds. A graphic display of the adduction displacement of the thumb was produced using a strip recorder.

Thiopental 3–5 mg/kg was given IV for induction of anesthesia in all patients. On loss of consciousness, stimulation of the ulnar nerve was begun and the control height of muscle twitch was obtained. Succinylcholine 1.5 mg/kg lean body weight was then administered IV. The subjects' tracheas were intubated using cricoid pressure when evidence of full muscular relaxation was obtained (no demonstrable activity with nerve stimulation). With the use of a mass spectrophotometer, ventilation was then assisted to maintain end tidal CO_2 as close as possible to 45 mm Hg. The correlation between end-tidal CO_2 and arterial partial pressure of CO_2 was verified with arterial blood gases. Times were then recorded to the onset of attempted respiration by the patient as noted on the CO_2 tracing of the mass spectrophotometer. This time to onset of respiration was reinforced by observing gross movement of the reservoir bag and abdominal or thoracic excursion. Also recorded were the times to first evoked muscular response with nerve stimulation and times to 50 and 100% recovery of full twitch height. There was no fade evident on the train-of-four ratios on all patients, thus demonstrating return of function expected with a depolarizing type of neuromuscular blockade. All data and times recorded on all patients were performed by a single observer.

Anesthesia was maintained during the testing period with 50% N_2O/50% O_2 and intermittent low dose IV thiopental (25–75 mg). Most patients required no supplemental IV barbiturates during this period and no episodes of intraoperative recall were expressed on questioning during the postoperative visits. Narcotics and volatile anesthetics were used only after the testing period was completed.

Results

Table 1 summarizes the results obtained. As demonstrated, the duration of apnea and time to return to 100% recovery of twitch height correlates inversely with plasma cholinesterase activity level. Spearman rank tests were calculated for the inverse plasma cholinesterase level versus minutes of apnea and time to recovery of 100% muscle twitch activity. These correlation coefficients were 0.9290 ($P < 0.0001$) and 0.9096 ($P < 0.0001$), respectively, indicating a statistically significant relation.

Figure 1 demonstrates graphically the relation between plasma cholinesterase level and minutes to 100% twitch activity. It should be noted on this graphic display that there were two patients in which time to 100% twitch recovery (22 and 27 minutes) varied significantly from the linear relation obtained. These were in patients with no measurable cholinesterase activity. Because of the inability to obtain dibucaine numbers by our assay in patients with no plasma cholinesterase activity, perhaps a genotypically abnormal form of that enzyme was present in these two patients, causing the significant difference from the linear correlation obtained.

An interesting observation in our study was that the return of ventilatory efforts usually preceded the first twitch response with the nerve stimulator by a short interval of time. This is consistent with the fact that diaphragmatic function begins to recover from

Table 1. Duration of Apnea, Time to First Evoked Muscular Response, and Time to 100% Recovery of Twitch Height in Patients with Genotypically Normal Plasma Cholinesterase Activity

Plasma cholinesterase level (IU/ml)	Number of patients	Apnea (min)	First evoked muscular response (min)	50% Recovery of twitch height (min)	100% Recovery of twitch height (min)
0–3	12	10.6 ± 4.8*	10.6 ± 4.8	12.0 ± 4.8	13.9 ± 5.0
		(6.1–23.3)†	(6.0–23.0)	(7.5–24.3)	(9.1–27.1)
4–7	7	6.7 ± 0.8	6.9 ± 0.9	8.3 ± 0.9	10.1 ± 0.9
		(5.1–8.1)	(5.2–8.3)	(6.5–9.8)	(8.2–11.3)
8–12	12	4.7 ± 0.8	5.0 ± 0.7	6.6 ± 0.7	8.4 ± 0.7
		(3.6–6.2)	(3.9–6.3)	(5.5–8.0)	(7.2–9.9)
13–18	9	4.0 ± 0.6	4.0 ± 0.6	5.6 ± 0.8	7.5 ± 0.7
		(3.3–4.9)	(3.2–5.0)	(4.9–6.8)	(6.3–8.5)

*Mean ± SD.
†Range.

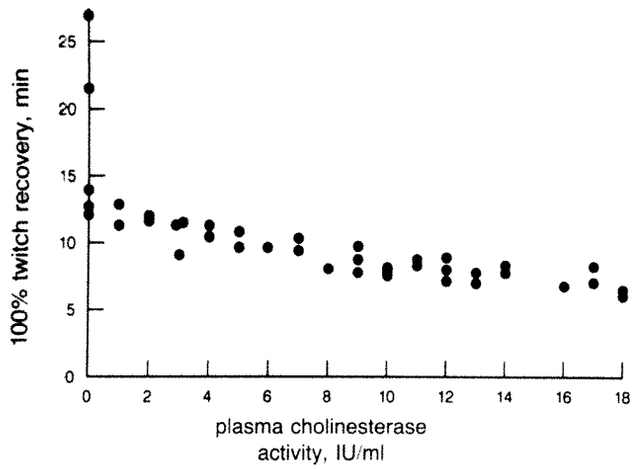

Figure 1. The relation between plasma cholinesterase activity and time to 100% recovery of twitch height after IV administration of succinylcholine 1.5 mg/kg lean body weight in 40 patients with normal enzyme genotypes.

succinylcholine neuromuscular blockade prior to evidence of return of peripheral muscle function (16).

Discussion

This study demonstrates that the duration of apnea and the time to 100% recovery of muscular twitch correlates inversely with plasma cholinesterase activity level, and that relation is highly statistically significant. This correlation is consistent with that found in the study of Viby-Mogensen in 1980 (10). In his investigation, however, all patients were premedicated with diazepam and were breathing halothane 0.75–1.50% during the testing period. Both drugs may alter the interpretation of the data in that study because of their muscle relaxant and/or respiratory depressant properties. In our investigation, no premedication was given and no volatile anesthetics were administered during the study. We also closely monitored the end-tidal CO_2 concentrations with the use of a mass spectrophotometer with results supported by measurement of arterial blood gas tensions. The use of the mass spectrophotometer allowed close monitoring of the end-tidal CO_2 and therefore ensured that we did not ventilate the subjects below the apneic threshold for $PaCO_2$. The mass spectrophotometer also allowed earlier recognition of the onset of respiration that might have been missed had movement of the reservoir bag been solely depended on.

Does the neuromuscular junction of the patient with chronic liver disease differ from the neuromuscular junction of normal patients? To our knowledge, no study yet performed has demonstrated a difference. This may allow the conclusion that this study, though performed on patients with chronic liver disease, may be applicable to any patient with genotypically normal cholinesterase deficiency. Several investigators have demonstrated that the nondepolarizing muscle relaxant requirements may be altered in patients with chronic liver disease due to increased volumes of distribution and/or altered metabolism (17–19). The patients in our study were assumed to have altered volumes of distribution secondary to their chronic liver disease. The dose of succinylcholine given was, therefore, based on calculated lean body weight and was sufficient to provide full muscular relaxation in all patients as determined with peripheral nerve stimulation. Whether altered volumes of distribution in our patients affected the results of our study cannot be determined because pharmacokinetic studies of succinylcholine are difficult to perform due to technical difficulties in measuring plasma succinylcholine levels.

Other genetic variant forms of plasma cholinesterase besides the dibucaine-resistant enzyme were not

investigated. The assay to determine fluoride inhibition is temperature-dependent and therefore difficult to perform. Also the calculated frequency of a homozygote for the fluoride-resistant gene is approximately 1 in 154,000 (4), making the possibility of its occurrence in this clinical investigation of 40 patients quite remote and its effect on our overall results quite minimal.

Our data demonstrating the times of duration of apnea and return to 100% muscle twitch activity are somewhat shorter than those found in previous studies (10). We believe this is most likely due to the fact that our patients received no medications pre- or intraoperatively that may have affected either the neuromuscular junction or the apneic threshold of CO_2. Our method of detection of time to onset of ventilatory efforts with the use of a mass spectrophotometer may also have allowed us earlier recognition of respiration.

In summary, we found an inverse correlation between plasma cholinesterase activity and the duration of action of succinylcholine. This relation may allow prediction of the length of succinylcholine apnea in patients with genotypically normal enzyme. Despite the absence of measurable cholinesterase activity, the longest time to 100% recovery of muscle twitch was 27 minutes. Therefore, except in surgical procedures of short duration, cholinesterase deficiencies in patients with genotypically normal enzyme should rarely be clinically relevant.

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Atracurium and Pheochromocytoma:

A Report of Three Cases

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Key Words: NEUROMUSCULAR RELAXANTS—atracurium. SURGERY—pheochromocytoma.

In patients with pheochromocytoma, the side effects of the neuromuscular relaxants involving the circulatory system become more pronounced and can be fatal (1). Although atracurium has been used without incident in two reported cases with pheochromocytoma (2,3), we describe a contrary experience. In our three patients, the injection of atracurium was associated with severe arterial hypertension, ventricular arrhythmias, and elevation of plasma catecholamine levels.

Case 1

A 66-year-old woman with a 4-year history of labile hypertension showed a left retrogastric mass on a CT scan of the abdomen. Plasma levels of epinephrine and norepinephrine were 3,661 and 2,813 pg/ml before clonidine, and 1,906 and 1,956 pg/ml, respectively, 3 hours after clonidine (4). During a hypertensive episode, plasma epinephrine was 22,000 pg/ml, suggesting a tumor secreting predominantly epinephrine.

The patient was given 2 units of whole blood preoperatively to increase her intravascular volume. No sympathetic blocking agents were used. Premedication was with oral diazepam 5 mg, IM meperidine 50 mg, and atropine 0.4 mg. In the operating room, IV sufentanil 50 μg was administered and a radial artery catheter was inserted. The arterial blood pressure (BP) was 200/100 mm Hg and heart rate (HR) 96 beats/min. Nitroglycerine 100 μg was given IV followed by infusion at a rate of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and BP decreased to 140/70 mm Hg. The HR was 70 beats/min. Anesthesia was induced with IV sufentanil 50 μg and thiopental 150 mg followed by 50% nitrous oxide in oxygen via a mask and concentrations of isoflurane up to 1% (expired). Ventilation was manually controlled and arterial blood gas tensions were in the normal range. Atracurium 0.7 mg/kg was then administered IV for 100% suppression of train-of-four stimulation within 1 minute. After a transient (30-second) episode of hypotension (BP 100/60 mm Hg), BP returned to pre-atracurium values but was associated with ventricular arrhythmias (Table 1). They were managed with an IV bolus of nitroglycerin 100 μg, lidocaine 50 mg, and a 5-minute respite from all stimulation before tracheal intubation. Plasma catecholamine levels were measured before and after administration of atracurium, during tumor manipulation, and after removal of the tumor (Table 2). Anesthesia was maintained with $N_2O:O_2$ (50:50) and isoflurane (1–2%) under controlled ventilation. Intravenous infusions of nitroprusside (1 to 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$), nitroglycerine (5 to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and 1 to 2 mg bolus injections of propranolol (total dose 20 mg) were used to control systemic blood pressure and ventricular arrhythmias during the 3.5 hours of surgery for removal of a retroperitoneal mass (Table 1). Pathologic examination showed the encapsulated mass (150 gm) to be an adrenal pheochromocytoma. Intraoperative fluid replacement consisted of 250 ml packed red cells, 500 ml 5% albumin, and 7600 ml of crystalloid solution.

At the end of the operation, the patient was monitored in the surgical intensive care unit. After 16 hours of elective mechanical ventilation, the trachea was extubated. During this period, the patient required a continuous IV infusion of nitroprusside 1 to 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The remainder of the postoperative period was uneventful and 12 days later the patient was discharged from the hospital.

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Table 1. Systemic Arterial Pressure (BP) and Heart Rate (HR)

	Case 1		Case 2		Case 3	
	BP (mm Hg)	HR (beats/min)	BP (mm Hg)	HR (beats/min)	BP (mm Hg)	HR (beats/min)
Preoperative	140/80	100	156/100	78	166/110	115
Postinduction, 5 min before atracurium	150/70	70	160/80	86	190/100	120
5 Min after atracurium before laryngoscopy	160/60	76	190/100	126	240/150	90
5 Min before incision	160/86	72	180/102	70	130/80	98
5 Min after abdomen opened	180/90	70	176/90	75	125/80	99
During tumor manipulation	248/120	86	240/128	92	250/140	130
30 to 60 Min after tumor removal	118/60	72	130/80	82	110/62	96
7th postoperative day	126/90	100	130/80	92	140/90	90

Table 2. Plasma Norepinephrine (NE) and Epinephrine (E) Levels in Pg/ml*

	Case 1		Case 2		Case 3	
	NE	E	NE	E	NE	E
Preoperative	2,813	3,661	3,505	274	4,926	56
Postinduction 5 min before atracurium	1,493	2,514	2,060	242	3,809	131
5 Min after atracurium before laryngoscopy	2,697	9,574	9,126	688	15,446	701
5 Min before incision	1,901	9,022	8,119	1,612	6,401	268
5 Min after abdomen opened	1,742	5,504	14,001	5,950	6,282	258
During tumor manipulation	9,597	20,967	18,462	2,242	210,857	7,348
30 to 60 Min after tumor removal	8,648	12,917	1,144	220	20,544	735
7th postoperative day	910	114	247	45	326	18

Normal Value N.E. 218 ± 92 SD and E 48 ± 12 SD.

Case 2

A 46-year-old woman with a 4-year history of hypertension was referred because combinations of hydrochlorthiazide, atenolol, and captopril had failed to control her BP. A CT scan of the abdomen revealed a 3-cm well circumscribed mass in the area of the left adrenal gland. Plasma levels of epinephrine and norepinephrine were 274 and 3,305 pg/ml before clonidine and 329 and 3,146 pg/ml 3 hours after clonidine, respectively (4).

Preoperatively, the patient was treated with prazosin HCl 2 mg three times a day and transfused with 2 units of packed red blood cells. Premedication consisted of oral diazepam 5 mg, IM meperidine 75 mg, and atropine 0.4 mg. Diazepam 10 mg and sufentanil 50 μg were given intravenously during insertion of a radial artery catheter. An IV bolus injection of nitroglycerine 80 μg was given to decrease system arterial hypertension before induction of anesthesia with IV thiopental 375 mg, $N_2O:O_2$ (50:50) and isoflurane (up to 3%) by mask. Under stable cardiovascular and respiratory conditions (manual ventilation), atracurium 0.6 mg/kg was given intravenously. The BP decreased briefly, but increased spontaneously over the next 30 seconds from 120/70 to 190/100 mm Hg (Table 1). This was easily managed with IV nitroprusside (two 50-μg bolus injections). After a 5-minute period without stimulation, laryngoscopy and tracheal intubation were accomplished. Anesthesia was maintained with isoflurane (0.2 to 3%) and $N_2O:O_2$ (50:50). During the 2.5-hour resection of a left adrenal pheochromocytoma weighing 15.8 gms, IV nitroglycerine 6 mg (in 50- to 100-μg bolus injections), nitroprusside infusion (40 mg), and propranolol 2.5 mg (0.5-mg bolus injections) were used. Intraoperative fluid therapy consisted of hetastarch 500 ml and crystalloids 3,750 ml. The postoperative course was unremarkable and the patient was discharged from the hospital on the ninth postoperative day.

Case 3

A 26-year-old woman, 1 month postpartum, was referred after an intrapartum hypertensive crisis. A pheochromocytoma was suspected because of elevated urinary levels of norepinephrine plus epinephrine (6,998 μg/24 hours, normal up to 135) and metanephrine (18.7 mg/24 hours, normal 0.3 to 0.9).

She was treated with oral propranolol 40 mg and dibenzylin 10 mg twice daily. Four days before surgery, both these drugs were discontinued and replaced with prazosin HCl 2 mg four times a day. Two units of whole blood were given to increase intravascular volume. Preoperative increased plasma catecholamine levels (Table 2), CT scan of the abdomen and I-131 MIBG study confirmed the presence of a tumor in the region of the left adrenal gland (4).

The patient was premedicated with meperidine 50 mg IM and oral diazepam 10 mg. In the operating room, with IV diazepam 10 mg and fentanyl 100 μg sedation, a radial artery catheter was inserted and an IV bolus of 100 μg nitroglycerine and 50 mg lidocaine was given to lower the BP and suppress ventricular ectopy. Anesthesia was induced with IV fentanyl 100 μg and thiopental 125 mg, and $N_2O:O_2$ (50:50) and enflurane (1%) by mask. Ventilation was manually controlled. Arterial samples were drawn 5 minutes before and after administration of atracurium (0.6 mg/kg) but before laryngoscopy and tracheal intubation. Despite incremental doses of nitroglycerine (100 μg) and an intravenous infusion of nitroprusside (3 $\mu g \cdot kg^{-1} \cdot min^{-1}$) the BP reached 240/150 mm Hg and HR 90 beats/min before laryngoscopy (Table 1). Tracheal intubation was accomplished under stable hemodynamic conditions by increasing the nitroprusside infusion up to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Anesthesia was maintained with enflurane (up to 2%) and $N_2O:O_2$ (50:50). After 2.4 hours of surgery the encapsulated left infrarenal mass was confirmed to be a paraganglioma. Intraoperative fluid therapy consisted of 500 ml of hetastarch and 4,400 ml of crystalloids. During the procedure, nitroprusside 1 to 4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and nitroglycerine 1 to 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ were infused to maintain BP between 120/70 and 140/90 mm Hg. A total of 6.8 mg propranolol was used to treat ventricular arrhythmias. At the end of the procedure, neostigmine and atropine were administered before removal of the endotracheal tube. The patient was transferred to the recovery room where she remained hemodynamically stable. Vasodilators, antiarrhythmics or vasopressors were not required. She was discharged 7 days after the operation.

Discussion

The normal adrenal medulla resembles an enlarged sympathetic ganglion. Its cells, responding to nicotinic innervation, release catecholamines by exocytosis. Pheochromocytoma and paraganglioma are catecholamine-secreting tumors made up of pheochromocytes. Neurohormone release from such tumors, however, is likely to be a result of numerous stimuli including anxiety, hypoxemia, hypercarbia, hypoglycemia, muscular exercise, and mechanical pressure (5). Nonanaesthetic agents that have been implicated in stimulating hormone release include acetylcholine and histamine.

Cardiovascular responses to neuromuscular blockade in patients with pheochromocytoma and the underlying pharmacologic mechanisms are complex, variable, and poorly understood. Moreover, only two published reports to date relate neuromuscular blockade to changes observed in plasma catecholamine concentration (2,6). Compounds with a structural similarity to acetylcholine may show a nicotinic action. This group includes succinylcholine, which may also effect catecholamine release secondary to muscular fasciculation (7). Pancuronium has been used successfully during resection of pheochromocytoma, although tachycardia and hypertension have occurred after large doses. These hemodynamic changes are thought to be due to a sympathomimetic action of pancuronium. In a recent case report, atracurium was found to cause little or no change in circulation or plasma catecholamine concentrations in a patient with pheochromocytoma (2).

Histamine release as a cause of intraoperative hypertension in patients with pheochromocytoma requires special consideration because 1) the basis of an earlier provocative (and dangerous) diagnostic test for pheochromocytoma (8) and, 2) histamine is an extremely active substance capable of mimicking a variety of physiologic and pharmacologic phenomena. Histamine release is a common feature of many drugs used in anesthetic practice. It is also one of the primary mechanisms suggested as the cause for the cardiovascular changes observed after the administration of nondepolarizing muscle relaxants. Atracurium can be associated with release of histamine (9). Administration of 0.6 mg/kg atracurium was associated with histamine release in 45% of young healthy adults (10). The range of plasma histamine was 0.5 to 5 ng/ml (mean 2.5). In humans a plasma histamine level of 5 ng/ml will result in two-fold increases in plasma epinephrine and norepinephrine (11). Marked increases in circulating catecholamines and a secondary rise in blood pressure is known to occur in patients with pheochromocytoma after IV bolus injections of as little as 10 μg histamine (8). Even though plasma histamine levels were not measured in our patients, the blood levels of histamine associated with atracurium are in the same general range as blood level of histamine administered exogenously that are associated with increase in catecholamine levels. The apparent discrepancy between our find-

ings and those of Stirt et al. (2) may be explained by the work of Barnes et al. (10), which indicates that the effects of atracurium on histamine release is influenced by both the absolute dose as well as the rate of administration of the drug.

There may be alternative explanations for the observed intraoperative hemodynamic and plasma catecholamine changes. In all three cases, meperidine was used for premedication at least 1 hour before induction of anesthesia. Meperidine is also a histamine releaser. It is possible that the anticholinergic action of atropine premedication in cases 1 and 2 lead to uninhibited sympathetic activity, which will contribute to increased catecholamine drive. Because these drugs were administered at least 1 hour before induction of anesthesia, we consider it unlikely that they contributed to the intraoperative tachycardia, hypertension, and elevated plasma catecholamine levels. A reflex increase in sympathoadrenal medullary activity secondary to nitroprusside- and nitroglycerine-induced hypotension could increase blood levels of catecholamines (12,13). But in our three cases these agents were used to control acute hypertensive episodes and arterial pressure was maintained at near normotensive levels. However, this possibility cannot be excluded entirely.

The predominant catecholamine in the "resting" preoperative state was norepinephrine in patients 2 and 3; in case 1 levels of both neurohormones were elevated but epinephrine was the predominant amine. A similar balance remained after induction of anesthesia, 5 minutes before atracurium injection, when the circulating catecholamine levels were generally lower (Table 2). Before laryngoscopy, increases in plasma norepinephrine and epinephrine by approximately two-to-five–fold followed complete neuromuscular blockade with atracurium. As expected, arterial hypertension and circulating catecholamines reached peaks during tumor manipulation and epinephrine was elevated in all three patients. Whereas the pressures returned to normal levels 30 to 60 minutes after tumor removal, the plasma catecholamine concentrations did not (Tables 1 and 2). Overall there appeared to be an association between plasma norepinephrine and/or epinephrine, ventricular ectopy, and the level of arterial pressure.

Vecuronium, a monoquaternary derivative of pancuronium, apparently has little or no autonomic effects and does not release histamine. In three patients with pheochromocytoma, it produced minimal changes in arterial pressure and plasma catecholamine levels (6). This or a similar blocker may be eventually confirmed as a drug of choice. In the meantime, however, our findings fail to confirm atracurium as devoid of circulatory effects or catecholamine release in patients with pheochromocytoma.

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Letters to the Editor

Ulnar Nerve Palsy of Unusual Etiology

To the Editor:

We read with interest the letter by Gertel and Shapira (Anesth Analg 1987;66:1343) in which they report a case of postoperative ulnar nerve palsy due to pressure on the ulnar groove produced by a cutaneous electrode used for electrical stimulation of the ulnar nerve. The patient was a healthy 47-year-old man of large build whose left arm had been placed on an armboard in 80° abduction with the forearm and upper arm pronated, i.e., internally rotated. Due to the fact that the maximum output from their nerve stimulator was 30 milliamperes and the patient was a large man, one electrode was placed at the wrist and a second at the elbow, in the expectation that one of them would provide supramaximal stimulation.

First, to evaluate neuromuscular function properly, supramaximal stimulation of the nerve is mandatory (1). It is recommended that nerve stimulators designed for this purpose be capable of delivering pulses with amplitudes of no less than 50–60 milliamperes at all frequencies (2). Therefore, we doubt whether the nerve stimulator used by Gertel and Shapira would have produced any useful clinical information.

Second, we must disagree with their statement that "this complication is completely avoidable by placing the arm and forearm on the armboard in the externally rotated position." Excessive abduction coupled with external rotation, i.e., supination and dorsal extension of the arm when an arm board is used may injure the lowest root of the brachial plexus, T1, and produce what is known as Klumpke's paralysis (3). To minimize this, it is essential that external rotation as well as excessive abduction of the arm are avoided whenever an arm board is used (4). The correct use of a nerve stimulator giving supramaximal stimulation at the wrist would have avoided this complication.

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In Response:

Thank you for the opportunity to reply to the comments of Drs. Lee, Birkhan and Rosenberg on our report (1) of a complication.

It is precisely because of our awareness that in large patients one may not achieve supramaximal stimulation with cutaneous electrodes, both placed at the wrist, if the output of the nerve stimulator is only 30 milliamperes, that we attempted to overcome the problem by placing one electrode over the ulnar nerve groove at the elbow. One has to work with what is available. The nerve stimulators available to us have an output of 30 milliamperes. We have noticed that in many large patients (and indeed in some normal-sized patients) we can achieve a considerably larger twitch response in the ulnar-innervated muscles of the hand when we place the distal electrode at the wrist and move the proximal electrode to the ulnar groove at the elbow, where the nerve is superficial even in obese patients. Having done this, one can often improve the mechanical twitch response even further by feeling for the ulnar nerve, and precisely holding the electrode over it with gentle finger pressure. This is easily achieved because the skin in this area is very mobile. While we have not conclusively proven that we achieve supramaximal stimulation with this technique, we undoubtedly do so in at least nearly all patients. We did not advocate excessive abduction of the arm and can only agree that prevention of one complication should not result in another.

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Flapper Valve Malfunction

To the Editor:

We read with interest the recent Clinical Report by Khalil et al. (1) in which inadequate ventilation of two patients was attributed to "malfunction of the flapper-valve of the scavenger valve" when an Ohio Modulus I anesthesia machine with a free-standing Ohio fluidic model number 800 ventilator was used. We wish to make several comments.

First, the valve whose failure is described is the ventilator relief valve, which compensates for the continuous introduction of fresh gas into the breathing system. This valve closes during inspiration, directing all gases to the patient circuit, and opens during expiration after the bellows has refilled, permitting excess gas to leave the circuit. Although the excess gas which is released may enter a waste-gas scavenging system, this relief valve is an integral part of the ventilator and not part of the scavenging system, as is suggested in the Title, Introduction, and Discussion sections of the report (1).

Second, the problem described may well have existed prior to being noticed during case #1. Thus, for a 60-kg patient, the initial ventilator settings were a tidal volume of 900 ml and a rate of 11 breaths/min. A predicted tidal volume of 15 ml/kg and minute ventilation of 9.9 L at the outset appear excessive unless deliberate hyperventilation was desired. This seems unlikely for the orthopedic procedure described.

Third, the authors stated that "the ventilator and the scavenger system were carefully and repeatedly checked by several anesthesia personnel during and after the case, but there was no apparent gas leak" (1). It would be of interest to know what type of scavenging system and interface was being used and exactly how the checks were performed. Modern closed active scavenging systems interface gas which has been dumped from the patient circuit with the hospital suction system. Waste gas enters the scavenging system via the ventilator relief valve or the adjustable pressure limiting ("pop-off") valve in the patient circuit. The rate at which this gas is removed by the hospital suction is controlled by adjusting the amount of suction applied using a screw valve on the interface. The interface also incorporates positive and negative pressure relief valves, and a distensible reservoir bag (2). The positive pressure relief valve opens to permit release of gases into the room if the rate of delivery of gas to the interface exceeds its rate of removal by the suction system. The negative pressure relief ("pop-in") valve(s) allow entrainment of room air when the pressure in the interface falls below atmospheric.

The distensible reservoir bag acts as its name suggests, but it is also used to adjust optimally and monitor the function of the scavenging system (2). In such an optimally adjusted and normally functioning system, the scavenger reservoir bag increases in size during positive pressure ventilation only at the end of the expiratory phase of ventilation when excess gas is released from the patient circuit, and decreases in size only during the inspiratory phase. These fluctuations in volume of the reservoir bag are, however, a function of the fresh gas flow rate from the anesthesia machine, the respiratory rate, and the I:E ratio set on the ventilator since these are the factors that determine the volume of gas released from the patient circuit at the end of each expiration. Changes in reservoir bag size can be made more obvious if the scavenging interface is temporarily disconnected from the hospital suction so that waste gas is no longer actively removed. In this situation, the obvious distension of the scavenging reservoir bag during the inspiratory phase of positive pressure ventilation would suggest the type of malfunction (incompetence) of the ventilator relief valve described. In the two incidents reported (1) the leaks were certainly significant since case #1 (23-year-old male, 60 kg) required a minute ventilation of 15 L, and case #2 (45-year-old female, 60 kg) 13.5 L, to maintain adequate end-tidal and $PaCO_2$ levels. Leaks of such a size would most likely be detectable by observing the scavenging reservoir bag during inspiration.

Fourth, there is clearly a need to check carefully the function of both the ventilator and the scavenging systems. The authors state that "Normally ventilator and exhaust system are not included in the circuit as part of [the] check list and it is almost impossible to design a preoperative check that would pick up this particular problem" (1). However, ventilator and scavenger are indeed included in the Anesthesia Apparatus Checkout Recommendations published by the Food and Drug Administration (FDA Checkout Procedure, August 1986, item 18d). Proper performance of this checkout demands that the ventilator be tested with the patient end of the circuit attached to a "test lung" in the form of a reservoir bag. Large gas leaks from the ventilator can be detected during this checkout by noting a large discrepancy between the preset tidal volume on the ventilator and the amount of gas actually delivered, as demonstrated by the volumeter in the breathing circuit. Had this check been performed, leaks of the magnitude described would surely have been detected. A check for leaks in the breathing circuit, which revealed none in bag mode but a large leak in ventilator mode, localizes the problem to the ventilator and its connections to the breathing circuit. Once the malfunction has been discovered, the ventilator should be serviced before being returned to clinical use.

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Book Review

Radiology for Anesthesia and Critical Care

Christine H. Murphy and Michael R. Murphy, eds. New York: Churchill-Livingstone, 1987, 273 pp, $50.00.

Imaging modalities are essential for the management of critically ill and postoperative patients. Anesthesiologists depend on various imaging techniques for decision making in the operating room, recovery room, and critical care units. In recent years, anesthesiologists have been called upon to care for patients undergoing both invasive and noninvasive procedures in the radiology suite. In addition, radiologic techniques are a useful adjunct in the performance of nerve blocks and placement of catheters for pain therapy. Clearly a text that addresses the wide gamut and efficacies of the currently available imaging modalities would serve a useful purpose.

Radiology for Anesthesia and Critical Care provides only a limited introduction to the multi-faceted uses of imaging techniques in the critical care setting and seems to be primarily derived from a chapter, "Radiology of the Chest," written by our authors for Doctors Murphy—in *Thoracic Anesthesia* (Churchill-Livingstone, 1983). Many images from that book were incorporated into this text, and there is heavy emphasis on plain film chest radiology. In general, the plain film radiographic images are of high quality and illustrate important and common diagnostic entities such as pulmonary edema, pneumonia, atelectasis, pulmonary embolism, ARDS, and abnormal tube positions. The examples of each diagnostic entity are appropriate and clearly explained. In addition, the chapters discussing the basic principles of plain film radiography in adults were complete and well done.

The 84 pages devoted to neonatal and pediatric problems are especially good. The tables of differential diagnosis of respiratory distress in the neonate, congenital heart disease, and pulmonary problems in infants and older children were extensive. The chapter on the neonate in distress provides useful correlative laboratory values of interest to the critical care physician as well as indications for surgery. Each point discussed is nicely illustrated with high quality images. The pathophysiology of congenital heart problems and many pulmonary parenchymal problems in the child are clearly explained. Lacking is mention of more complex lesions demanding early surgical intervention such as hypoplastic left heart syndrome and the various forms of truncus arteriosus. Postoperative complications in the pediatric cardiology patient are not discussed, but the reader is told the findings are similar to those in adults. If a primarily pediatric intensivist is using the book as a reference, this exclusion can be disconcerting, especially with the special challenges regarding fluid balance in the pediatric patient.

The chapter on the pediatric airway includes several helpful images. However, several of the entities listed are not discussed—nor the radiographic signs explained. The problems encountered by the anesthesiologist due to nasopharyngeal adenoid hypertrophy in children are not mentioned. Although many differential diagnoses are listed, no differential radiographic features are provided. There is, however, a comprehensive discussion of the fluoroscopic findings of various causes of stridor.

The chapter on monitoring and life-support devices is comprehensive and logically arranged. In general, though, the illustrations are of poor quality with the exception of those demonstrating pacemakers.

Much of the remainder of the book is marred by superficial treatment of topics such as anesthetic considerations for invasive procedures, radiologic safety, radiology in the recovery room, and the treatment of iodinated contrast reactions. More serious is the lack of emphasis on the many currently available imaging modalities that are used for problem solving in critically ill patients. The few ultrasound images provided are outdated, and there appears to be a lack of appreciation of the multiple applications of sonography. For example, sonography is the modality of choice for the evaluation of intracranial hemorrhage in the infant with a patent anterior fontanelle; for deciphering an opaque hemithorax; for evaluating acquired and congenital heart diseases, including clarifying the underlying cause for cardiomegaly (cardiac and/or specific chamber enlargement vs pericardial effusion); diaphragmatic integrity and motion, localizing pulmonary abscesses and fluid collections in the chest for percutaneous drainage; demonstrating pulmonary agenesis; clarifying the underlying cause for abdominal distention (bowel loops vs ascites vs mass), evaluating the urinary tract in all age patients with anuria or decreased urine output and positions and complications of catheters (including intravascular, urinary stents, bladder catheters). There was no mention of the use of Duplex/Doppler ultrasound for assessment of vascular access routes or flow to vital organs.

Also lacking was discussion of the importance of com-

puted tomography in the evaluation of the airway, particularly for the diagnosis of airway compromise, tracheal and bronchial foreign bodies, congenital anomalies, and for differentiating the various causes of endotracheal and endobronchial lesions as well as tracheal compression.

Nuclear medicine is used for evaluation of brain death and anuria, but this is not discussed in the text. The uses of magnetic resonance imaging for evaluating the brain, spinal cord and epidural space are likewise not discussed.

Anesthesiologists involved in the management of pain problems use radiologic techniques for needle placement, catheter placement, and nerve blocks for pain therapy. The treatment of these topics is omitted from this text. Anesthesia for radiologic procedures, including the problems of delivering anesthesia for MRI studies is discussed in a superficial manner.

This book can be recommended as an introduction to the radiology of critically ill patients by means of plain film radiology primarily. The modern intensivist cannot rely solely on this book to familiarize him/herself with the expanding role of modern imaging techniques. The book would be especially useful for medical students and housestaff during the early period of their rotation in a critical care unit, especially given the reasonable cost of the text. The book is printed on high quality paper and is easy to read.

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Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Brown BR Jr: Anesthesia in Hepatic and Biliary Tract Disease, FA Davis Co., Philadelphia, 1988. 300 pp, $58.00

Chart T: Computing for Clinicians, IOP Publishing Ltd, Bristol, 1988. 136 pp, $32.40

Civetta JM, Taylor RW, Kirby RR: Critical Care, J. B. Lippincott Co., Philadelphia, PA, 1988. 1754 pp, $99.00

Fyman P, Gotta AW: Controversies in Cardiovascular Anesthesia, Kluwer Academic Publishers, Boston, 1988. 192 pp

Ghia JN (ed): The Multidisciplinary Pain Center, Martinus Nijhoff Publishing, Boston, 1988. 185 pp, $40.95

Gravenstein JS, Holzer JF: Safety and Cost Containment in Anesthesia, Butterworths, Boston, 1988. 257 pp, $22.95

Rosen M, Lunn JN (eds): Consciousness, Awareness, and Pain in General Anesthesia, Butterworths, Boston, 1987. 195 pp, $34.95

Watkins J, Levy CJ: Guide to Immediate Anaesthetic Reactions, Butterworths, Boston, 1988. 128 pp, $21.95

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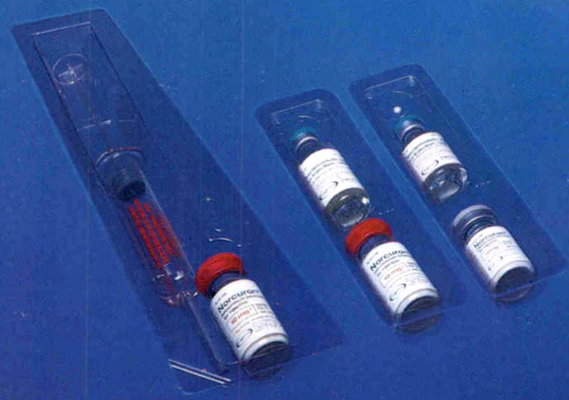

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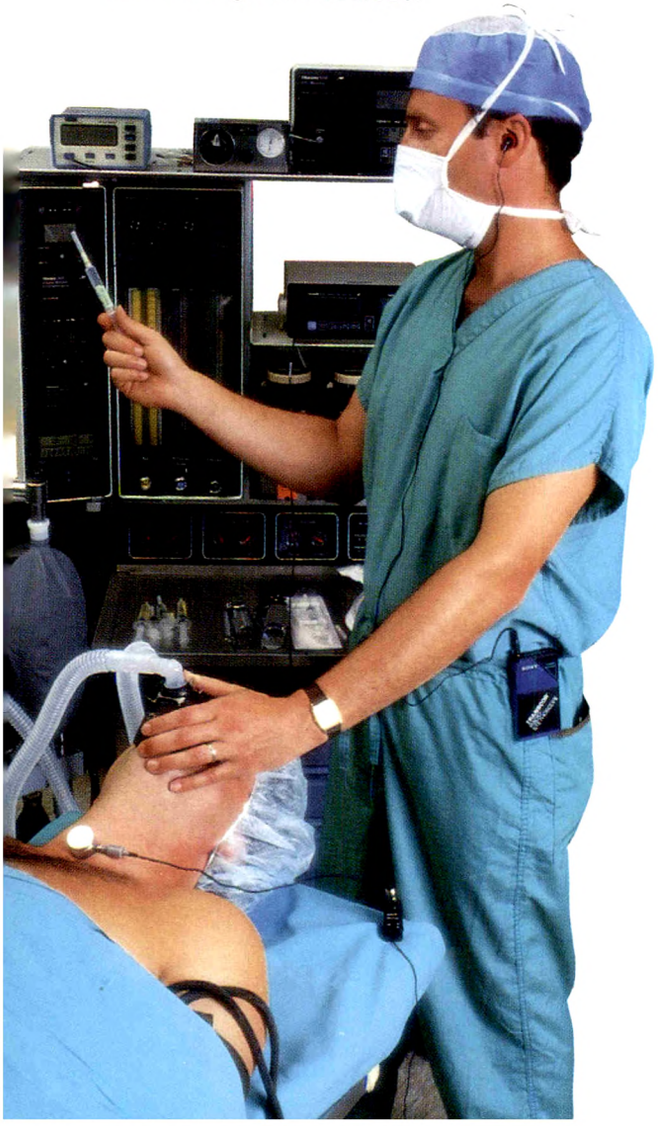

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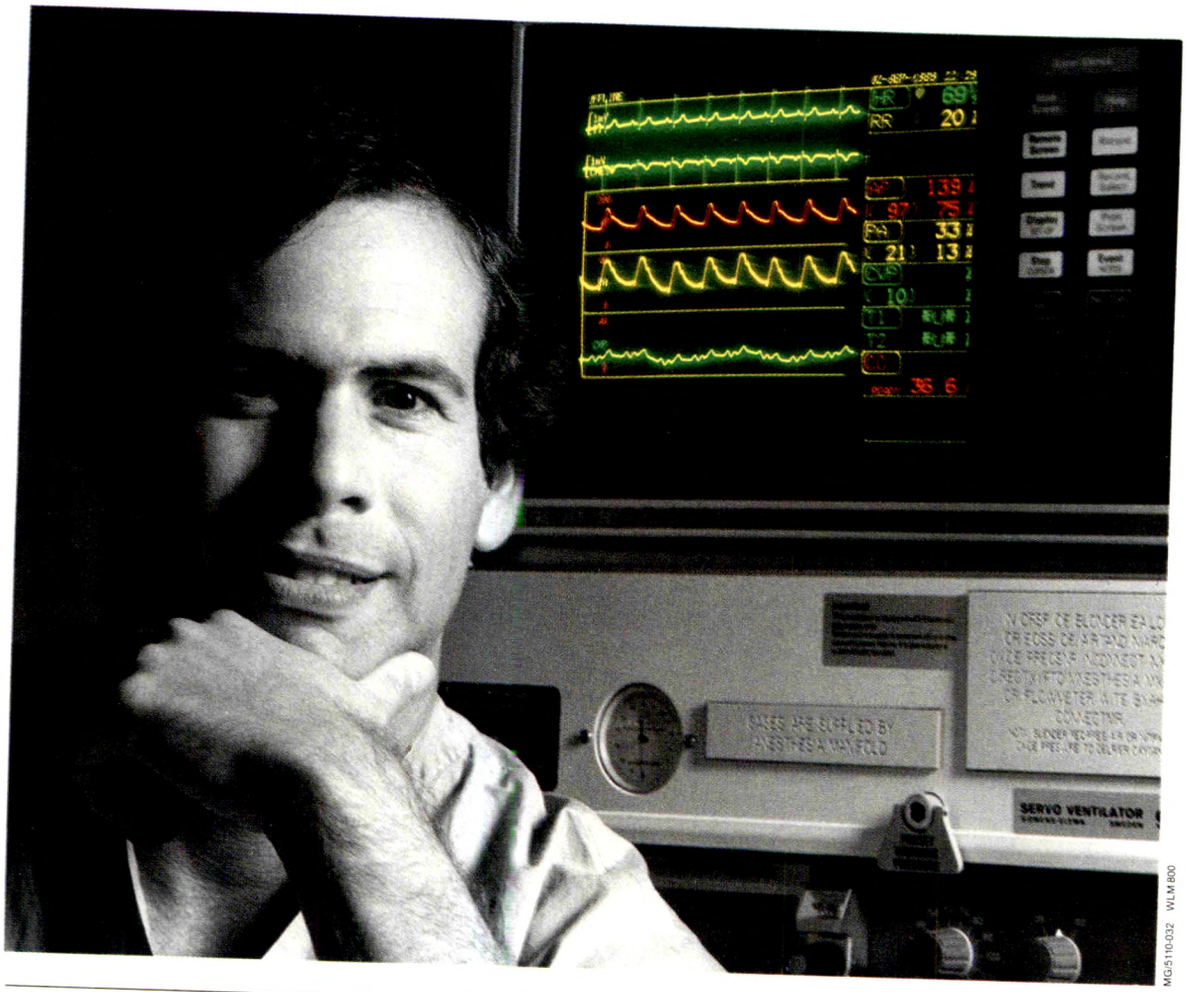

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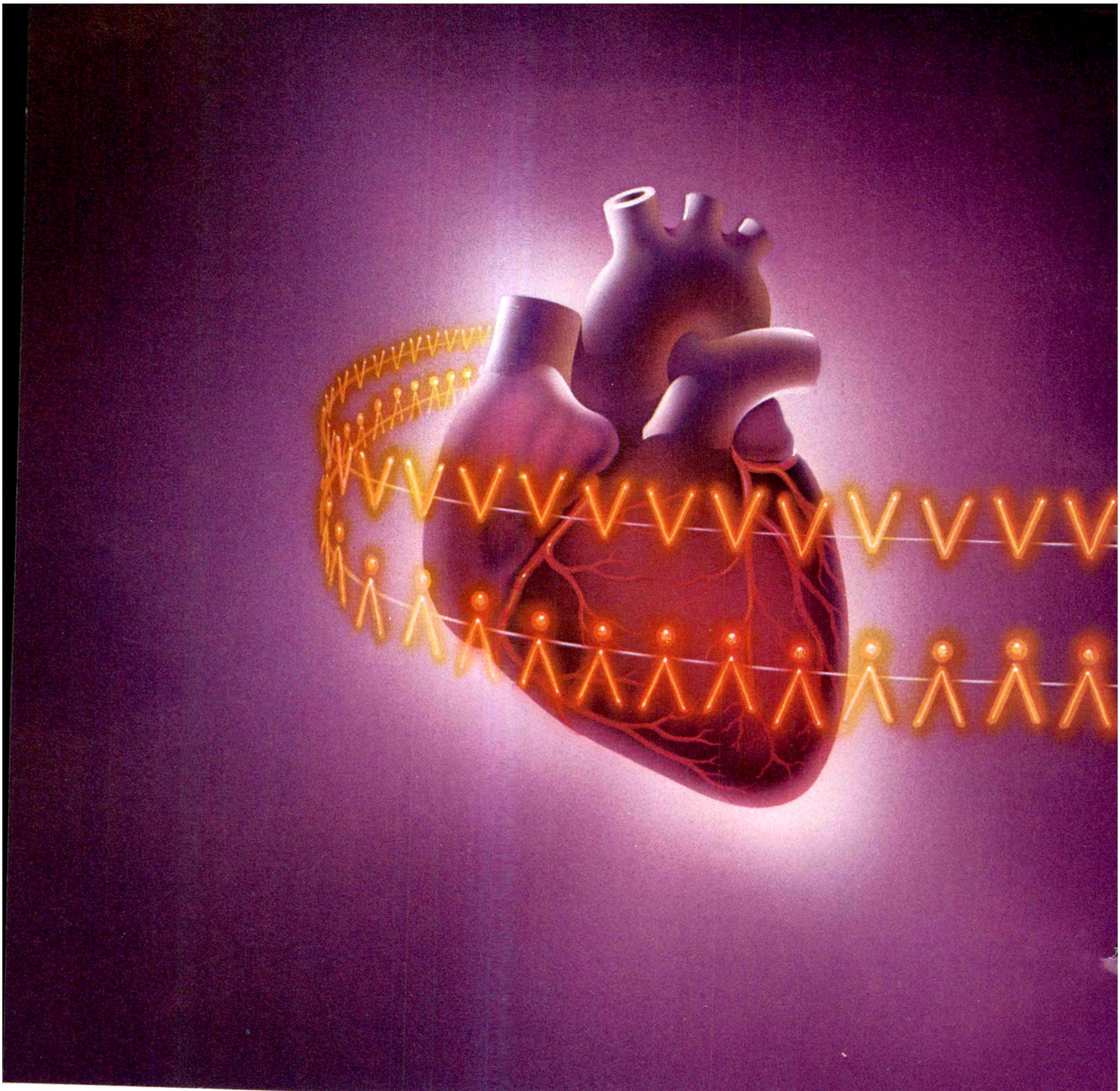

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Editorial

Pain Mechanisms in Lumbar Radiculopathy

Stephen E. Abram, MD

Key Words: PAIN, SCIATICA. ANESTHETIC TECHNIQUES, REGIONAL—sciatic block.

Xavier et al (1) have reported a series of patients with symptoms of lumbar radiculopathy who experienced days to weeks of pain relief following sciatic nerve block. A decade ago their results would have been seriously questioned, as they would have contradicted the current pathophysiological theories of the origin of pain associated with nerve root compression. Today, their findings are surprising, but not mystifying, since recent neurophysiological studies have provided us with some reasonable explanations of this phenomenon.

There has been a slow evolution of our understanding of the mechanism of the pain induced by disc herniation and radiculopathy. In 1934, Mixter and Barr (2) demonstrated a relationship between intervertebral disc herniation and sciatica. Their report heralded a long era of surgical management of sciatica. It seemed obvious that disc protrusion caused nerve root compression and that compression caused pain. Surgical removal of the disc should, ostensibly, relieve the pain. Unfortunately, this simple solution has not always proven effective. Hirsch and Nachemson (3) found that only 11% of 232 patients with sciatica were pain-free 2 years after surgery. Other studies report almost identical results. There must, therefore, be a more complex explanation of the pathophysiology of sciatica.

In 1977 Murphy (4) published a rather extensive treatise, based largely on anatomic studies, on the development of lumbar radiculopathy. He proposed that the herniated disc produces nerve root injury by either mechanical compression or chemical injury caused by substances released from the degenerating disc. In response to injury of the root, there is leakage of serum proteins into the endoneurial space. Since the endoneurial space is devoid of lymphatics, these proteins are cleared with difficulty. The exudate is invaded by inflammatory cells, and intraneural fibrosis ensues. There is, as a consequence of this process, a "choking out" of axons in the fibrotic area, altering the normal balance of nerve conduction, and a change in the biomechanical properties of the nerve, with loss of elasticity and inability of the nerve to stretch with leg or back motion. Pain results from activation of local nociceptors, the nerva nervorum, from artificial synapse formation in the region of the nerve root injury. Although intriguing, Murphy's theories fail to explain the phenomenon of pain relief with sciatic nerve block or the frequent failure of rhizotomy to relieve radicular pain.

At about the same time as Murphy's publication, Howe et al (5) reported a somewhat different theory of the origin of radicular pain, based upon neurophysiological rather than anatomic studies. They demonstrated that acute mechanical compression of a normal dorsal root in cats produced only brief firing of the nerve. In contrast, mechanical compression of the dorsal root ganglion (DRG) produced sustained, repetitive firing of the nerve, lasting several minutes. Likewise, mechanical compression of a chronically injured nerve root also produced sustained repetitive firing. The investigators found little evidence of spontaneous firing of injured nerve roots in the absence of mechanical stimulation. They concluded that radicular pain is associated with compression by the herniated disc of dorsal root ganglia or of chronically injured segments of nerve root. Unfortunately, these theories also fail to explain the pain relief by sciatic nerve block or the failure of rhizotomy to relieve pain.

Other pathophysiologic mechanisms involving the dorsal root and dorsal root ganglia have been suggested. Selective damage to large afferent fibers in the

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dorsal root by disc herniation might lead to central disinhibition of dorsal horn pain projection neurons, leading to enhanced ability of nociceptor activity to give rise to pain perception (hyperalgesia). In such a situation, nerve block distal to the site of nerve injury would be expected to reduce the hyperalgesia, but should have little influence on spontaneous pain. Wall and Devor (6) demonstrated spontaneous activity arising from dorsal root ganglia in rats following sciatic nerve section. Ectopic discharge from the ganglia was propagated both orthodromically and antidromically. Although their experiments did not include dorsal root lesions, it is at least theoretically possible that similar phenomena may occur following nerve root compression. Nordin et al (7) were able to record antidromically conducted showers of activity in the sural nerve of a patient with S1 radiculopathy during a painful straight-leg raising maneuver. It was presumed that the activity arose from the injured nerve root segment. Such antidromic activity may be responsible for changes in peripheral tissues that further aggravate pain. If C fibers are activated antidromically, peripheral release of substance P could result in vasodilation and changes in sensitivity of nociceptors in skin, muscle or other somatic structures (8). One would not expect sciatic nerve block to influence the perception of sensation resulting from orthodromic transmission of ectopic nerve root or DRG discharge, but the block could influence the tissue changes related to antidromic transmission

Since extensive deafferentation often fails to relieve pain of presumed peripheral origin and, indeed, may of itself produce severe, intractable pain, many investigators have sought central nervous system mechanisms to explain certain types of pain. In 1943, Livingston (9) proposed that loss of neuronal input set up circular, reverberating neuronal activity in the central nervous system that could eventually spread to increasing numbers of adjacent neurons. Such activity occuring in the pain projection system would be perceived as pain in the normal receptive fields of the involved neurons. Later investigators proposed that deafferentation led to hypersensitivity or even spontaneous firing of cells of origin of the spinothalamic tracts in the dorsal horn (10).

The most realistic explanations of pain associated with disc herniation and subsequent radiculopathy probably involve both peripheral and central mechanisms. Devor (11) has recently explored peripheral and central mechanisms that may relate to the phenomena of spontaneous pain and allodynia associated with peripheral nerve or nerve root lesions. He suggests that nociceptors may become sensitized in the periphery so that they fire spontaneously or are activated by weak stimuli. Nociceptors may also develop impulse generating capabilities at injured sites. Crosstalk at the level of nerve injury may result in activation of nociceptors by low threshold fibers (mechanoreceptors) at sites of demyelination. Local anesthetic block of the sciatic nerve distal to an injured nerve root would be expected to diminish activity arising from sensitized nociceptors and would limit inputs from low threshold afferents that activate nociceptors ephaptically at the site of the root lesion. Obviously peripheral nerve block would not affect spontaneous impulse generation from the injured segment.

Alterations in central processing must also take place, as evidenced by changes in the receptive fields of dorsal horn neurons that have been observed to occur soon after nerve injury (11). Two mechanisms for these changes in receptive fields have been proposed: 1) Following nerve root injury and consequent degeneration of afferent terminals in the dorsal horn, some of the lost synapses are replaced by new growth from fibers in neighboring intact dorsal roots. 2) Previously ineffective synapses with afferents from distant nerve roots become functionally effective following loss of neuronal inputs from the normal receptive field. Devor proposes that, under normal circumstances, certain dorsal horn neurons are driven mainly by nociceptors from a given receptive field. In addition, there are synapses with low threshold receptors (e.g. mechanoreceptors) both within and outside the normal receptive field, but these synapses are rather ineffective at activating a dorsal horn cell. A neuropathic process now attacks the neurons that normally activate this dorsal horn cell, disrupting normal trophic relations, and strengthens previously ineffective synaptic inputs. Now the remaining low-threshold afferents, both within and outside the original receptive field, drive the cell and the central pain circuit. The result is allodynia. Input from remaining nociceptors in the original and expanded receptive fields may also contribute to activation of pain projection systems, resulting in hyperalgesia. How would such a scheme respond to peripheral local anesthetic nerve block? Block of the sciatic nerve distal to the site of the nerve root lesion in a patient with radiculopathy could interrupt both nociceptors and low threshold afferents that now drive the central pain circuit.

Although we now have some plausible explanations of the relief of radiculopathic pain by sciatic nerve block, we have difficulty explaining the fact that analgesia in Xavier's patients far outlasted the duration of the local anesthetic. Livingston's explanation of central reverberating circuits that are driven

by peripheral noxious inputs (9) is a tempting one to invoke, but there is little experimental evidence for it. Another possible explanation of the prolonged analgesic effect of the blocks involves sensitization of wide dynamic range (WDR) neurons, multireceptive cells located in the dorsal horn that are part of the central pain projection system. There is ample evidence that WDR neurons are sensitized by activity in C-polymodal nociceptors (12). It is conceivable that the persistent abnormal inputs associated with radicular pain could result in similar WDR sensitization. Blockade of the ongoing barrage of afferent discharges may result in a return of WDR neurons to a normal level of sensitivity, leading to a prolonged absence of pain perception.

One might argue that the analgesia experienced by Xavier's patients represents a placebo effect. This seems unlikely because the responses reported were atypical of classical reaction to placebo. Generally, one expects about 35% of patients in a given population to react to a placebo, the analgesic effect is usually about 50% of the anticipated analgesic effect of the pain-relieving procedure, and the duration of response tends to be short-lived (13). In contrast, 100% of Xavier's patients experienced pain relief, relief of the radicular component of the pain was complete, and the analgesia lasted days to weeks. If the analgesia were related to placebo effect, one might expect diminution of back pain as well as sciatica, but that was not the case in the patients presented.

I agree with Xavier's contention that systemic effects of lidocaine are unlikely to account for the analgesic effect of the sciatic nerve blocks, particularly in light of the lack of appreciable effect from the same mass of lidocaine injected into trigger points. In addition, the blood levels achieved by perineural injection of 150 mg lidocaine are well below the blood levels achieved by investigators using intravenous lidocaine to relieve neuropathic pain. It also seems unlikely that perineural spread of the injected lidocaine could directly affect the injured nerve root segments. The drug would have to dissect cephalad for a distance of 20 cm or more, and enter the epidural space via the neural foramen.

Although this report provides us some possible insight into the pain mechanisms associated with lumbar disc disease, it seems unlikely that the technique will be of significant therapeutic benefit. There is a low but real risk of nerve damage with peripheral nerve blocks, and repeated local anesthetic blocks of the sciatic nerve have been reported to cause myositis, myelin vacuolization of the nerve, and impaired nerve function in animals (14). The real value of this report is to remind us of the tremendous complexity of the peripheral and central nervous system. We must refrain from drawing diagnostic or prognostic conclusions based upon the patient's response to local anesthetic blocks. It is obvious that we cannot differentiate between radiculopathy and peripheral neuropathy on the basis of response to peripheral nerve block. Extensive adverse experience has taught us that we can not predict response to surgical decompression or rhizotomy on the basis of selective nerve root blocks. Thinking of the pain projection system as a series of straight through neural pathways produces misconceptions about the source of a patient's pain and often leads to ineffective or disastrous modes of therapy.

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Influence of Bupivacaine as an Adjuvant to Epidural Morphine for Analgesia after Cesarean Section

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DOUGLAS MJ, McMORLAND GH, JANZEN JA. Influence of bupivacaine as an adjunct to epidural morphine for analgesia after cesarean section. Anesth Analg 1988;67:1138–41.

The effect of the addition of bupivacaine to epidural morphine (EM) on postoperative analgesia was evaluated in 150 patients after cesarean section performed under epidural anesthesia with carbonated lidocaine. Fifty patients received 3 mg EM without bupivacaine, 50 received 3 mg EM with 0.125% bupivacaine, 25 received 5 mg EM without bupivacaine, and 25 patients received 5 mg EM with 0.125% bupivacaine. Patients were assessed for quality and duration of postoperative analgesia, as well as the incidence and severity of side effects. The addition of bupivacaine did not affect the quality or duration of analgesia afforded by EM and did not influence the incidence or severity of side effects. Furthermore, there was no statistically significant difference in the analgesia obtained by patients receiving 3- and 5-mg doses of EM with or without bupivacaine.

Key Words: ANESTHESIA—obstetric.
ANESTHETIC TECHNIQUES—epidural.
ANALGESICS, MORPHINE—epidural.

A report by Hanson et al. (1) in 1984 suggested that the addition of bupivacaine 0.125% to epidural morphine (EM) led to a longer duration of postoperative analgesia with enhanced intraoperative analgesia and less nausea and vomiting than when epidural morphine in saline was used. They raised the question of possible synergism between the two agents. A 3-mg dose of EM was used in that study, an amount smaller than that commonly used in North America.

The purpose of this study was to compare, in a double-blind fashion, the effect of the addition of bupivacaine 0.125% to both 3-mg and 5-mg doses of epidural morphine on the duration and quality of analgesia after cesarean section and the incidence of postoperative side effects.

Methods

Following approval from the University of British Columbia Screening Committee for Research Involving Human Subjects, 100 ASA I–II patients presenting for elective cesarean section under epidural anesthesia were enrolled. Informed consent was obtained and, after an IV infusion of 1–2 L of lactated Ringer's solution, an epidural catheter was inserted at either the L2–3 or L3–4 level. All patients received carbonated lidocaine (1.73%) with freshly added 1:400,000 epinephrine via the epidural catheter for anesthesia. This was administered incrementally, after a 3-ml test dose, to produce anesthesia to the T4 dermatome. After the birth of the baby, the patients were randomly assigned to receive one of the following solutions: 5 mg EM in saline (n = 25), 5 mg EM in 0.125% bupivacaine (n = 25), 3 mg EM in saline (n = 25), 3 mg EM in 0.125% bupivacaine (n = 25)—all to a total volume of 10 ml. The EM plus bupivacaine solutions were prepared by adding 5 ml 0.25% bupivacaine to the appropriate amount of EM (Epimorph® 1 mg/ml) and sufficient saline (0.9%) to achieve a total volume of 10 ml. Both the patient and the anesthesiologist were unaware of the solution given. After surgery, the epidural catheter was removed. Each patient was asked to complete linear, visual analogue scales (0–10 cm) for pain and itching 3, 7, and 24 hours after EM injection. After the 24-hour period, the patients were visited and their charts reviewed to determine the incidence of nausea and vomiting, urinary retention,

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Table 1. Patient Characteristics

	3 + S* (n = 50)	3 + B† (n = 50)	5 + S‡ (n = 25)	5 + B§ (n = 25)
Age (yr)	31.8 ± 0.7	30.7 ± 0.6	31.7 ± 1.0	29.9 ± 0.8
Height (cm)	160 ± 1.1	158 ± 0.9	159 ± 1.0	161 ± 1.5
Weight (kg)	73 ± 2.7	74 ± 1.4	75 ± 2.2	76 ± 2.4
% Nulliparas	22%	24%	12%	20%
Total Local Anesthetic (ml)	18.3 ± 0.4	17.5 ± 0.4	17.0 ± 0.7	17.7 ± 0.6

Values are expressed as mean ± SEM.
Differences not significant at $P < 0.05$.
*3 mg EM + saline;
†3 mg EM + bupivacaine;
‡5 mg EM + saline;
§5 mg EM + bupivacaine.

lowest respiratory rate, time and type of first analgesic medication, and any other medications received.

After completion of the initial 100 patients, it was apparent that analgesia had been adequate in all study groups, and an additional 50 patients randomly received either 3 mg EM with 0.125% bupivacaine (n = 25) or 3 mg EM without bupivacaine (n = 25), and were followed up according to the protocol described earlier.

Data were analyzed for statistical significance using one-way analysis of variance-randomized groups, χ^2 analysis, and the Kruskal-Wallis test. $P < 0.05$ was considered statistically significant.

Results

The patient groups were similar with respect to age, height, weight, and total volume of local anesthetic solution injected (Table 1). The duration of analgesia was 27.4 hours for 5 mg EM in bupivacaine, 22 hours for 5 mg EM in saline, 24.4 hours for 3 mg EM in bupivacaine, and 23.3 hours for 3 mg EM in saline. Using one-way analysis of variance, there was no statistically significant difference between these times. The duration of analgesia in the additional 50 patients (25 in each of the 3-mg groups) was not significantly different from the two 5-mg groups (Table 2).

Only one of the patients received parenteral narcotic analgesia during the 24-hour study period. This patient was in the 3 mg EM + saline group; the narcotic was administered 17 hours after EM injection. Using χ^2 analysis to examine the number of patients with pain scale measurements of less than 3, 3–6, and greater than 6, there was no qualitative difference in analgesia among the four groups (Table 3). This was confirmed using the Kruskal-Wallis test. None of the patients had a respiratory rate <12 breaths/min. The incidence of postoperative nausea

Table 2. Duration of Analgesia after Cesarean Sectio

	Duration of Analgesia (hr)	
	(n = 25)	(n =
3 + S	23.3 ± 2.2	23.0
3 + B	24.4 ± 2.1	22.3
5 + S	22.0 ± 1.7	-
5 + B	27.4 ± 2.0	-

Values are expressed as mean ± SEM.
Differences are not significant at $P < 0.05$.
See Table 1 for abbreviations.

Table 3. Percentage of Patients in Different Pain Sco Categories 3, 7, and 24 Hours after Cesarean Section

Group	3 + S (n = 50) (%)	3 + B (n = 50) (%)	5 + S (n = 25) (%)	5 + (n = 25
Pain Score 3 hours				
< 3	75	78	71	88
3–6	21	18	25	8
>6	4	4	4	4
Pain Score 7 hours				
<3	88	80	84	92
3–6	10	18	8	4
>6	2	2	8	4
Pain Score 24 hours				
<3	72	48	60	72
3–6	22	34	24	16
>6	6	18	16	12

Differences are not significant at $P < 0.05$.
See Table 1 for definition of abbreviations.

Table 4. Postoperative Side Effects and Thearapy

Group	3 + S (n = 50)	3 + B (n = 50)	5 + S (n = 25)	5 (n
Mean Respiratory Rate	16.3	16.6	16.5	1
Nausea (%)	12	12	8	2
Vomiting (%)	40	34	52	3
Medication for pruritus (%)	20	36	28	2
Medication for nausea and vomiting (%)	28	24	25	4

Differences are not significant at $P < 0.05$.
See Table 1 for definition of abbreviations

and vomiting, severity of pruritus, and medica received for pruritus or nausea were not signific different among the four groups (Table 4). patients in the 5 mg EM + saline group and patients in the 3 mg EM + saline group had to a bladder catheter reinserted. The catheters initially removed in these patients in the reco room, which was the standard practice of their o

trician. Three patients (two in the 5 mg EM + bupivacaine group and one in the 3 mg EM + saline group) had no additional postoperative analgesia during their hospital stay. Data on duration of analgesia used in statistical analyses extended to 48 hours postoperatively at the most.

Discussion

The effectiveness of epidural morphine in the management of pain after cesarean section has been well established (2–10). Anesthesiologists have, however, been concerned with the optimal dose of EM and reduction of the incidence and severity of its side effects.

Hanson et al. (1) suggested that the addition of bupivacaine to epidural morphine improved both intraoperative and postoperative analgesia and decreased the incidence of side effects. They reported improved intraoperative analgesia in the patients who received the EM–bupivacaine combination. Because they did not examine a control group (bupivacaine alone), it is difficult to attribute this improvement to the combination of EM and bupivacaine as opposed to the effect of bupivacaine alone. They also found the incidence of nausea and vomiting 10–50 minutes after EM administration (intraoperatively) to be lower in the EM–bupivacaine group. Because of the variability in our hospital with respect to surgical technique, we did not examine intraoperative events (pain, nausea, and vomiting). It was difficult to control surgical maneuvers that might be expected to affect such intraoperative events in the number of patients examined. However, because Hanson et al. (1) did find an improvement in the duration of postoperative analgesia with the combination of morphine and bupivacaine, as well as a nonsignificant decrease in pruritus postpartum, this study sought to confirm their results.

Our results, using a different protocol, differed from those of Hanson et al. (1). We did not confirm a statistically longer duration of action of epidural morphine when it was combined with bupivacaine, nor did we show a difference in the incidence of postoperative side effects. There may be several reasons for this. First, the local anesthetic used for the cesarean section differed. Hanson et al. used bupivacaine 0.5% without epinephrine, whereas we used carbonated lidocaine with 1:400,000 epinephrine. It has been previously demonstrated (11) that the addition of epinephrine to the local anesthetic for surgical anesthesia increases the incidence and severity of epidural morphine-induced pruritus. In volunteers, Bromage (12) showed that epinephrine added to epidural morphine increased the duration of analgesia and the severity of all side effects.

Second, the Hanson study included patients who presumably had less than adequate surgical anesthesia (both of their groups contained patients who required general anesthesia or intravenous supplementation with ketamine, meperidine, diazepam, or nitrous oxide). Our protocol eliminated any patients who required more than 150 μg intravenous fentanyl intraoperatively. We used no other intraoperative sedatives or analgesics.

Finally, their study used a higher concentration of bupivacaine in their EM–bupivacaine combination. This certainly would have influenced intraoperative analgesia and may also have contributed to an extension of the local anesthetic-induced analgesia into the immediate postoperative period.

There has been considerable interest in the use of combinations of epidural opiates and local anesthetics (in particular, fentanyl–bupivacaine) to improve analgesia, to decrease the amount of local anesthetic used, and to decrease the incidence and severity of side effects. Numerous studies have examined surgical and labor analgesia while less attention has focused on these combinations for postoperative analgesia.

Cohen et al. (13) examined the effects of varying concentrations of fentanyl with bupivacaine on labor pain. They found that the addition of fentanyl did not significantly improve analgesia as compared to bupivacaine alone. Rucci et al. (14) examined bupivacaine–fentanyl combinations for surgical anesthesia in healthy male patients and found prolongation of analgesic blockade only when 200 μg was added. They also showed less motor block and less shivering when fentanyl was added. Gaffud et al. (15), in a similar study in patients having elective cesarean sections, found improved intraoperative analgesia. All of these studies suffer from numbers of patients too small in view of the demonstrated interpatient variability with respect to epidural narcotics (16).

A recent study by Logas et al. (17) examined continuous thoracic infusion of either saline, morphine, bupivacaine, or a combination of morphine and bupivacaine for analgesia after thoracotomy. Their results showed that a continuous infusion of either morphine alone or morphine–bupivacaine epidurally provided excellent analgesia. There was no statistically significant difference between the two groups with respect to analgesic effectiveness. Although they used a continuous technique, this study agrees with our results showing equivalent analgesia

with either epidural morphine or a morphine–bupivacaine combination.

A noteworthy finding in our study was the excellent analgesia produced by 3 mg epidural morphine, with or without bupivacaine. Previous studies (2–10) have reported on the use of ≥5 mg epidural morphine. Studies in which <4 mg epidural morphine were used (2,3,18) did not demonstrate good, long-lasting analgesia. Two exceptions were studies from Europe (1,19) that showed good analgesia with 3 mg epidural morphine. Our study was designed to examine not only the effect of bupivacaine added to the epidural morphine, but also to examine the duration and quality of analgesia provided by the lower dose of epidural morphine. The unexpectedly good analgesia provided by the 3-mg dose may, in fact, be partly attributable to the addition of epinephrine to the local anesthetic. Most previous studies, including those that found that doses <4 mg were ineffective, used local anesthetics without epinephrine (2,3,18). Because it is now common practice to add epinephrine (if only for the test dose), results of the present study are applicable to the current practice.

Although no demonstrable effect on the incidence and severity of side effects was shown by decreasing the dose of epidural morphine, it may be that in individuals who are particularly sensitive to narcotics a lower dose might be beneficial. Rosen et al. (2) demonstrated that more adverse side effects were seen in patients who received 5 or 7.5 mg EM than in those who received 2 mg.

In summary, this study showed that the addition of 0.125% bupivacaine to epidural morphine (3 and 5 mg) for analgesia after cesarean section had no effect either on postoperative analgesia or on the incidence and severity of side effects of EM. The finding that the 3-mg dose of epidural morphine provided a duration of analgesia similar to that of the 5-mg dose may be of benefit in that, potentially, the troublesome and rare life-threatening side effects of EM may be avoided by using the smaller dose.

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SMS 201–995 and Provocation Tests in Preparation of Patients with Carcinoids for Surgery or Hepatic Arterial Embolization

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AHLMAN H, ÅHLUND L, DAHLSTRÖM A, MARTNER J, STENQVIST O, TYLÉN U. SMS 201–995 and provocation tests in preparation of patients with carcinoids for surgery or hepatic arterial embolization. Anesth Analg 1988;67:1142–8.

Patients with midgut carcinoids undergoing surgical resection or ischemic treatment of hepatic metastases by embolization are at risk for development of carcinoid crises due to release of hormonally active tumor products. Eight such patients were treated on nine separate occasions with increasing subcutaneous doses of a synthetic somatostatin analogue (SMS 201–995) 4 days prior to surgery or hepatic arterial embolization. The patients were tested by pentagastrin provocation and simultaneous measurement of serotonin (5-HT) levels in peripheral blood before and after prophylactic treatment, to evaluate the efficacy of SMS 201–995. The provoked release of 5-HT was markedly diminished, and the basal levels of 5-HT were markedly reduced in patients with high initial levels. During surgery or embolization both SMS 201–995, as well as ketanserin, a 5-HT$_2$ receptor blocker, were given. With this combined treatment all patients were hemodynamically stable during surgery or embolization. During embolization the arterial levels of 5-HT increased only moderately, while urinary excretion of 5-hydroxyindoleacetic acid remained unchanged despite a proven adequate embolization. Two patients were operated on without previous treatment with SMS 201–995; both developed severe crises at induction of anesthesia, but IV SMS 201–995 rapidly reversed the bronchoconstriction and facial flush and gradually restored arterial blood pressure, even though cardiac output remained depressed for a prolonged period. The crisis reaction correlated well with high circulating levels of 5-HT, but after treatment with SMS 201–995 these levels were still high. These findings indicate that the acute IV administration of SMS 201–995 can antagonize the peripheral actions of 5-HT and tachykinins, an effect different from the reduced release seen after prophylactic treatment with SMS 201–995. SMS 201–995 may block an intracellular mechanism common for activation of monoamine and tachykinin receptors on both tumor cells and normal cells, which would explain the observed effects. The prophylactic use of SMS 201–995 is recommended prior to surgery or hepatic arterial embolization in patients with disseminated midgut carcinoid tumors, because peripheral blockade of 5-HT$_2$ receptors alone is not sufficient to prevent a crisis reaction.

Key Words: SEROTONIN, CARCINOID—5-HT antagonist. SURGERY, ABDOMINAL—carcinoid. ANESTHESIA—carcinoid excision.

Synthetic somatostatin analogues have been used both chronically and acutely to relieve symptoms caused by excessive secretion of tumors producing biogenic amines and tachykinins, in patients with the carcinoid syndrome (1,2). Acute administration of such drugs may rapidly provide protection against the peripheral actions of serotonin (5-HT) and/or peptides (2). Prophylactic use of somatostatin analogues in patients with the carcinoid syndrome has been suggested to prevent severe reactions caused by the release of tumor products during surgery and hepatic arterial embolization (3). Clinical and experimental studies (4,5) suggest that chronic treatment with a somatostatin analogue (SMS 201–995) may have effects additional to those seen with the acute administration of the drug; i.e., suppression of basal plasma levels of 5-HT and inhibition of provoked release of 5-HT (3).

The purpose of the present investigation was to study patients with the carcinoid syndrome to deter-

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Table 1. Preoperative 5-HIAA Levels in Urine and Peak/Basal Ratio of Peripheral Venous 5-HT Levels at Provocation with Pentagastrin before and after Treatment with SMS 201–995

	5-HIAA/urine* (before)	5-HT/peripheral vein† (before)	5-HT/peripheral vein† (after SMS 201–995)
Embolization patients			
EA (M 56)‡	54	351/234 = 1.50	224/213 = 1.05
NS (M 65)	17	235/104 = 2.26	108/76 = 1.30
SN (M 55)	19	368/185 = 1.99	158/129 = 1.22
RF I (F 55)	120		598/517 = 1.16
RF II	82	—	666/477 = 1.40
Surgery patients			
EL.A (F 73)	14	731/393 = 1.86	304/249 = 1.22
AG (F 60)	23	295/178 = 1.66	154/142 = 1.08
AS (F 66)	18	331/137 = 2.42	203/188 = 1.08
LL (M 57)	92	787/520 = 1.52	362/295 = 1.23
Mean		1.89 ± 0.14	1.19 ± 0.04

*ref. < 5 mmol/mol creat.
†< 150 ng/ml.
‡Sex (male/female) and age.

mine: 1) the effect of prophylactic treatment with SMS 201–995 on the peripheral levels of 5-HT during preoperative provocation tests; and 2) hemodynamic and biochemical responses during subsequent surgery or hepatic arterial embolization. In addition, in one patient who had two major surgical tumor reductions 2 months apart, the biochemical and hemodynamic parameters were studied on one occasion during selective blockade of peripheral 5-HT_2 receptors and on the other occasion during additional blockade with SMS 201–995.

Methods

Patients

All eight patients had a midgut carcinoid syndrome due to disseminated disease with severe diarrhea and daily facial flushes. In addition to metastases in mesenteric lymph nodes and liver, two patients (E.A., R.F.) also had peritoneal carcinoidosis. Physical examination, electrocardiography and chest x-ray were negative for evidence of cardiac valvular disease. At the time of study the patients were subject to either partial surgical resection of the tumor or subsequent treatment of hepatic metastases by unilateral hepatic arterial embolization (Table 1). All patients except L.L. were previously subjected to surgical debulking including dissection of central mesenteric lymph nodes and intestinal resection and, in certain cases, wedge resection of the liver. These procedures were combined with cholecystectomy and division of collateral vessels to the liver in preparation for subsequent embolization (6). One patient (R.F.) was studied during two embolizations (Table 1). In another patient (L.L.), the carcinoid disease also involved the pancreas and spleen and two operations were planned: one involving the intestine and the mesenteric lymph nodes, the other the pancreas and spleen. No patient had been given cytotoxic treatment or interferon therapy.

Anesthesia

In patients undergoing *embolization*, epidural catheters were placed at L1–2 or L2–3. Patients were awake during embolization. A catheter was placed in one of the hepatic arteries via the right femoral artery, which was punctured in local anesthesia. The embolization (Spongostan powder) caused pain in the right upper quadrant of the abdomen and nausea due to liver ischemia. Initially these symptoms were treated with small doses of fentanyl IV (0.05–0.1 mg). When hemodynamic stability had been observed for 20–30 minutes, pain relief was accomplished by epidural anesthesia (0.025% bupivacaine).

In patients undergoing *surgical* tumor reduction, anesthesia was induced with thiopental, fentanyl, nitrous oxide, and pancuronium in two patients, while midazolam, fentanyl, nitrous oxide, and vecuronium was used in the other two patients.

Provocation with Pentagastrin

All patients had preoperative provocation tests using pentagastrin (PG) (0.6 μg/kg IV). The levels of 5-HT in peripheral whole blood were determined under basal conditions and 1, 3, and 5 minutes after injection, using a highly specific and accurate technique of

Table 2. Arterial 5-HT Levels and Urinary 5-HIAA Levels Before, During, and After Hepatic Arterial Embolization

	5-HT-levels (ng/ml) in radial artery					5-HIAA levels (mmol/mol creat) in urine/ 6 hrs	
		Postembolization (min)					
	Basal	2	5	10	20	Basal	Postembolization
Patients							
EA	224	192	264	218	231	27	*
NS	145	136	136	154	181	4	5
SN	132	119	218	224	277	7	5
RF I	220	116	367	322	—	38	*
RF II	418	374	550	534	631	91	108

*Interference with analyses due to precipitations.

liquid chromatography with electrochemical detection (7). The provoked release of 5-HT was expressed as the ratio between the highest level after injection and the mean basal level of 5-HT (peak/basal ratio). The PG-test was performed at admission and repeated after treatment with SMS 201–995 on the day before surgery or embolization.

Treatment with SMS 201–995 and Ketanserin

SMS 201–995 (Sandoz, Basle, Switzerland) was administered according to the following protocol: 50 μg SC twice daily for 2 days and 100 μg SC twice daily for the next 2 days. Provocation with PG was then repeated. During surgery or embolization SMS 201–995 (100 μg × 4 SC) was given as well as the selective antagonist of peripheral 5-HT_2 receptors (ketanserin two IV 20-mg injections, Janssen Pharmaceuticals, Beerse, Belgium). Postoperatively SMS 201–995 (two 100-μg SC injections) was given for 2 days followed by two 50-μg SC injections daily until oral feeding started.

The initial treatment of one patient (R.F.) has previously been reported (3). This patient again developed carcinoid symptoms after surgery and embolizations over 8 months and was then treated chronically with SMS 201–995 (50 μg SC twice a day) chronically. At admission for repeated embolization the dose of the drug was increased to two 100 μg SC 2 days embolization. In this patient, PG tests were performed only on the day before embolization (Table 1).

All patients treated with embolization were given broad-spectrum antibiotics (8), while patients undergoing abdominal surgery were given one injection of doxycyclin 0.2 mg IV preoperatively.

Use of SMS 201–995 and ketanserin was approved in each individual patient by the Swedish National Board of Health and Welfare. Informed consent was obtained from each patient.

Table 3. Central Venous and Arterial Levels of 5-HT in a Patient (L.L.) with Carcinoid Crisis during Surgery

	5-HT levels (ng/ml)	
Stage of surgery	Superior caval vein	Radial artery
1* Before anesthesia	278	220
2 Skin incision	380	514
3 Facial flush	307	251
4 Bronchoconstriction	453	785
5 Tumor manipulation	898	922
Clinically stable, surgery continued	659	582
Surgery finished	469	282

*1–5 refer to indications in Figure 2.

Monitoring of Peripheral Arterial 5-HT Levels and Urinary 5-HIAA Levels during Embolization or Surgery

All patients undergoing embolization had a catheter placed in the radial artery for blood sampling. Under basal conditions repeated blood samples were withdrawn and, after embolization, samples were drawn at 2, 5, 10, and 20 minutes for measurement of 5-HT levels. Each patient had an indwelling urinary bladder catheter and urine was collected in two 6-hour periods, one period before and one period during and after embolization. 5-HIAA levels were determined in each urine collection (Table 2).

One patient (L.L.) undergoing primary surgery with selective blockade using ketanserin had a central venous catheter with the tip just above the right atrium as well as a radial arterial catheter. This patient was followed up with blood samples for 5-HT determination during various stages of surgery (Table 3).

Monitoring of the Clinical Effect of Hepatic Arterial Embolization

Embolization was performed using spongostan powder and was monitored by fluoroscopy. The proce-

dure was terminated when injected contrast medium stayed in the main arterial branches for more than 30 seconds (9). After embolization all patients developed an increased white cell count, slight fever reaction, and elevated blood levels of transaminases.

Hemodynamic Monitoring

Arterial and central venous blood pressures were recorded by indwelling catheters in the radial artery and superior caval vein, respectively. Cardiac output was monitored by impedance cardiography (MOMED NCCOM 3). Oxygen saturation was measured by pulse oxymetry (Novametrics 500).

Results

Preoperative Provocation with Pentagastrin

The peak/basal ratio of peripheral venous levels of 5-HT during provocation with PG was determined in seven patients on admission and in eight patients on nine separate occasions after pretreatment with SMS 201–995. On admission all patients tested developed carcinoid symptoms (gastrointestinal, facial flush) associated with PG provoked release of 5-HT. After pretreatment with SMS 201–995, the symptomatic response was absent or reduced and in the seven patients with previous PG-tests, the peak/basal ratio was markedly reduced. The mean ratio before treatment was 1.89 ± 0.14, which was significantly ($P < 0.01$) reduced to 1.19 ± 0.04 after treatment with SMS 201–995 (Table 1).

Basal levels of 5-HT were significantly reduced ($P < 0.05$) in the seven patients studied before and after SMS 201–995. This reduction was most prominent in the two patients with very high levels of 5-HT (EL.A. and L.L.) (Table 1).

Peripheral Arterial Levels of 5-HT and Urinary 5-HIAA at Hepatic Arterial Embolization

In four patients studied on five separate occasions, the peripheral arterial levels of 5-HT were followed before and up to 20 minutes after embolization. During this period all patients developed nausea and pain and the arteriograms indicated an adequate embolization. On three separate occasions 5-HT levels exceeding basal levels by 50% were recorded. No substantial increase or urinary 5-HIAA levels were monitored in any of the patients. In two of the patients it was not possible to analyze postoperative urine for 5-HIAA due to presence of an unidentified precipitation product (Table 2).

Hemodynamic Responses during Embolization/ Surgery

Mean arterial blood pressure, cardiac output, and systemic vascular resistance were little influenced by embolization in the four patients pretreated with SMS 201–995 and ketanserin (Fig. 1). No changes in oxygen saturation were recorded.

Four patients with SMS 201–995 and ketanserin pretreatment underwent 4- to 6-hour operations for surgical debulking without hemodynamic disturbances. One patient (L.L.) had this combined pretreatment and first underwent intestinal resection with central lymph node dissection and cholecystectomy. This patient had a distal pancreatectomy and splenectomy 2 months later with only ketanserin treatment. Anesthesia was induced with fentanyl (0.1–0.2 mg) and midazolam (15 mg) on both occasions. Muscle relaxation was achieved by vecuronium (5 mg). Shortly after the skin incision the patient had a vivid flush reaction accompanied by a moderate decrease in arterial blood pressure. When the abdomen was opened the patient developed a carcinoid crisis with severe flushing and bronchoconstriction, a critical decrease of arterial blood pressure and cardiac output accompanied by a decreased systemic vascular resistance (Fig. 2). In this situation 100 μg SMS 201–995 was injected IV, which promptly reversed flushing and bronchoconstriction and restored arterial blood pressure. The increase in arterial blood pressure was mainly due to an increase in peripheral vascular resistance. Surgery was discontinued for 20 minutes and before further surgery a second dose of SMS 201–995 (150 μg SC) was given. The planned surgical procedures were thereafter performed without changes in arterial blood pressure. The crisis reaction correlated well with very high levels of 5-HT in arterial blood (Table 3). After injection of SMS 201–995 and continued surgery, the 5-HT levels remained high despite a clinically stable situation with maintained arterial blood pressure. At the end of surgery the 5-HT levels had returned to initial values, while cardiac output remained depressed and systemic vascular resistance was increased. The early postoperative course was uneventful.

Discussion

Cytotoxic drugs (streptozotocin, adriamycin, 5-fluorouracil) have no certain therapeutic value in the

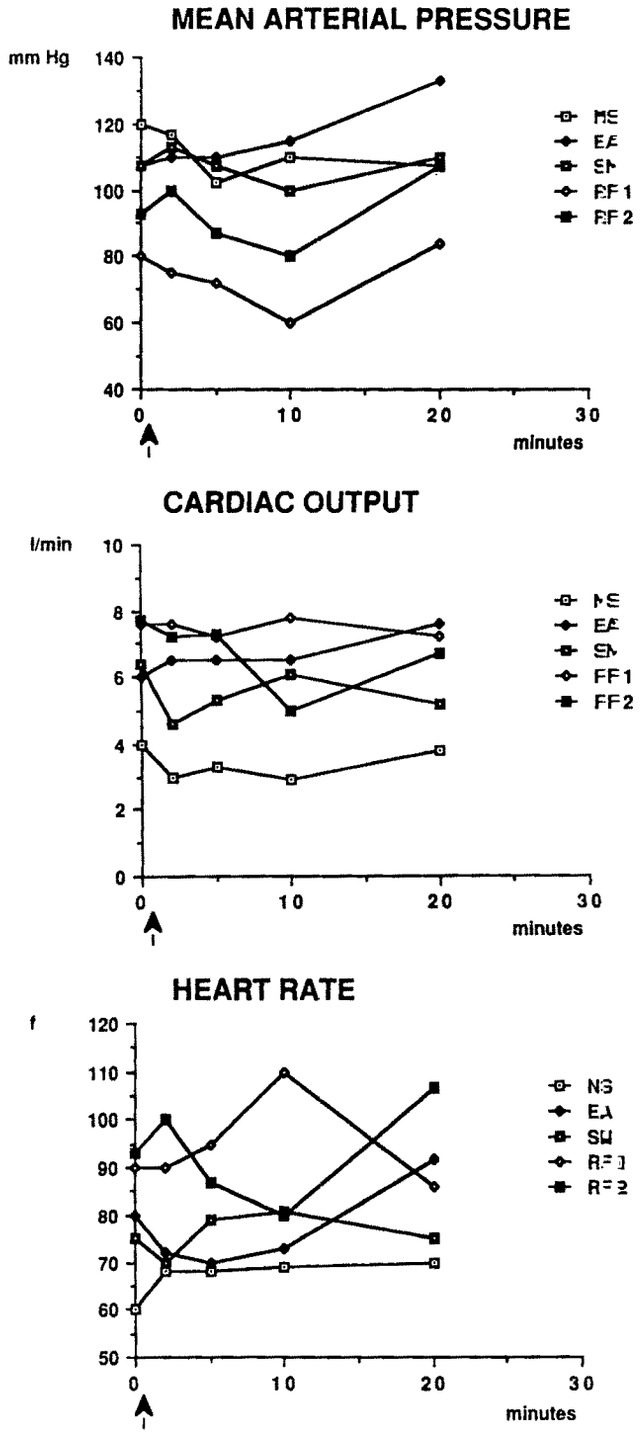

Figure 1. Hemodynamic monitoring before and after hepatic arterial embolization in patients after pretreatment with SMS 201–995. Arrows indicate injection of embolization material.

treatment of disseminated intestinal endocrine tumors (10,11). Because carcinoid lesions in the liver are chiefly supplied by blood from the hepatic arteries, several techniques to establish hepatic ischemia can be applied. Using a *surgical* technique to cause a temporary dearterialization of the liver (12), the hemodynamic changes caused by liberated tumor products can be reversed by release of the hepatic artery occlusion. One alternative technique to establish ischemia is *transarterial embolization* of the hepatic arteries (6). This method may be more effective, because the entire arterial tree is temporarily filled with the embolization material. If hemodynamic disturbances occur secondary to embolization, treatment of hypotension, including use of corticosteroids, is necessary. Another problem is pain after embolization; if the patient develops a low arterial blood pressure, epidural anesthesia for relief of pain should be avoided to avoid the risk of decreasing arterial pressure further. However, no such reaction was seen in our embolization patients, and so epidural analgesia was used without adverse hemodynamic effects. Catecholamines released from the adrenals and sympathetic neurons most likely have a pathogenetic role in the crisis reaction by causing release of tumour products (13). Adequate pain relief is therefore desirable to reduce the stress response. The risk of carcinoid crises in patients with large tumor masses undergoing surgical debulking procedures is considerable. Special care is needed during anesthesia (14) and during mechanical manipulation of the tumor masses. One of the embolization patients (R.F.) had previously had a severe carcinoid crisis with an attempt to induce anesthesia (3). After pretreatment with SMS 201–995 in combination with ketanserin this patient subsequently underwent major surgical debulking and hepatic arterial embolizations on four separate occasions with stable hemodynamic parameters.

Prophylactic use of a somatostatin analogue (SMS 201–995) with subsequent challenge of this blockade by PG is a new approach in an attempt to prevent reactions described earlier. This somatostatin analogue, in combination with ketanserin during embolization or surgery, was successfully used in the present series of patients with disseminated midgut carcinoid tumours. One mode of action of SMS 201–995 is its influence on the spontaneous release of 5-HT from the carcinoid lesions; the basal levels of 5-HT were reduced during treatment. In all patients SMS 201–995 also markedly reduced the release of 5-HT provoked by PG, resulting in little or no symptoms during these preoperative provocative tests. This inhibitory effect is most likely due to SMS 201–995, because ketanserin does not inhibit PG-provoked release of 5-HT (7). The somatostatin analogue most probably has a similar action on the release of other tumour products of midgut carcinoid tumours, e.g., tachykinins. Tachykinins are also lib-

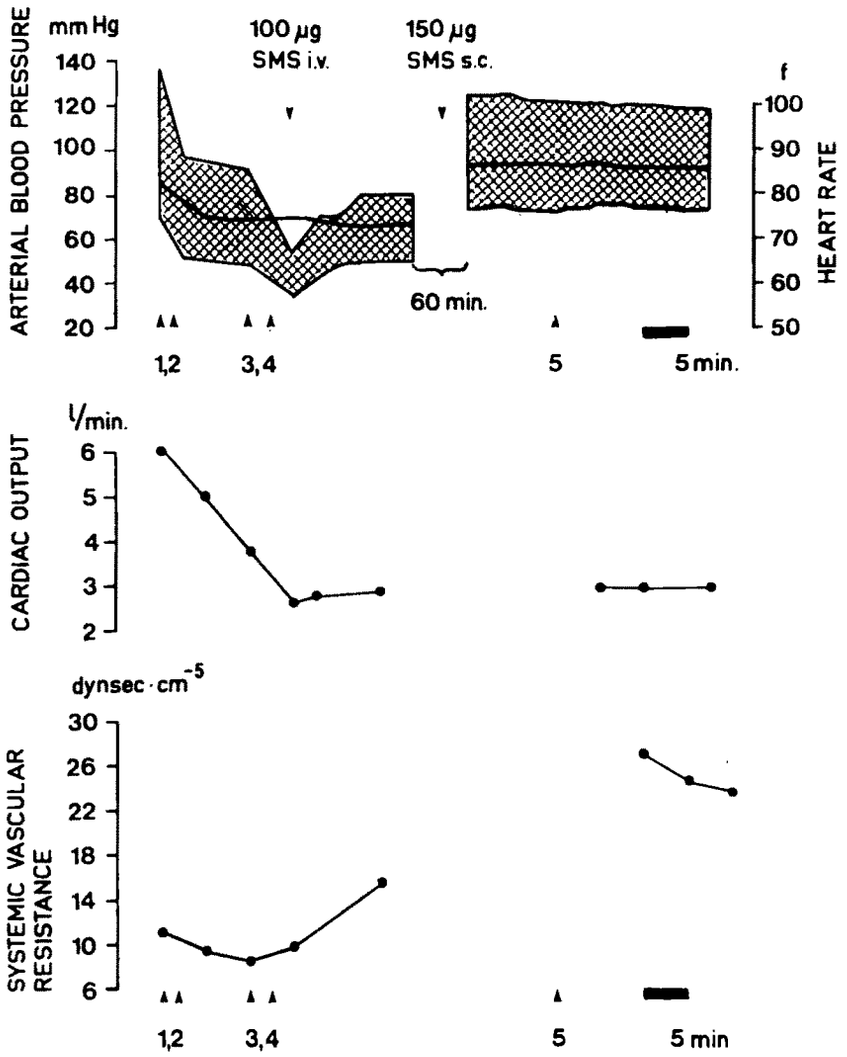

Figure 2. Hemodynamic monitoring of a patient (L.L.) who developed a carcinoid crisis during anesthesia and surgery (see text and Table 3).

erated by PG and may contribute to the flush reaction (15). During the first 20 minutes after embolization, peripheral levels of 5-HT were only moderately elevated. Furthermore, no evident changes were seen in the 5-HIAA levels over 6 hours in association with embolization, despite an angiographically and clinically proven adequate embolization in all patients. These findings therefore indicate an inhibition of the release of 5-HT during and after embolization.

The exact site of action of SMS 201–995 is not known, but on the basis of our observations the following hypothesis is presented. The signal to fast cellular responses exerted by several hormones and monoamines is mediated across the cell membrane via phosphatidylinositol and its phosphates (PIP), which in turn mobilize intracellular calcium. Activation of receptors for polypeptides with trophic actions only occasionally generates PIP and diacylglycerol. Such receptors penetrate the cell membrane and when activated the signal is transformed as an increase in phosphorylation at the intracellular domain (1). The individual design of signal transformation across the cell membrane for different hormones may be a clue to the site of action of SMS 201–995. PG has an indirect mode of action by causing release of catecholamines from the adrenals, which in turn activate adrenoreceptors on carcinoid tumor cells (13). If the signal transformation via PIP for certain substances, e.g., catecholamines, 5-HT, and tachykinins, is impaired by SMS 201–995, this might explain the low release from the tumor cells observed spontaneously or at PG stimulation. The somatostatin analogue most probably exerts similar effects on other cells than tumor cells, which might explain the effects seen in the crisis situation with diminished responses to circulating catecholamines, 5-HT, and tachykinins. Evidently the time course for onset of effects by SMS 201–995 on tumor cells (3) and normal cells (Fig. 2) differ, the former responding more slowly.

One patient (L.L.) had two surgical procedures

performed (similar in duration of surgery and in amount of tumor manipulation). When treated only with ketanserin to produce peripheral blockade of 5-HT_2 receptors, this patient developed a severe crisis reaction that was reversed with SMS 201–995 IV. The discrepancy between 5-HT levels in simultaneous samples from artery and superior caval vein most probably reflects periods of excessive release of 5-HT. During such periods the pulmonary clearance of 5-HT is exceeded, leading to relatively higher levels on the arterial side. Sampling from the superior caval vein only indirectly reflects release of 5-HT from the tumor region, which drains into the inferior caval vein. 5-HT levels in the superior caval vein can not therefore be directly compared with the arterial levels. When pretreated with both SMS 201–995 and ketanserin, surgery and anesthesia were uneventful. The clinical outcome in this patient clearly demonstrates that other substances than 5-HT are involved in the crisis reaction. Furthermore, acute administration of the somatostatin analogue has peripheral effects additional to the inhibited release of tumour products, leading to stabilization of arterial blood pressure despite high circulating levels of 5-HT (see earlier). This peripheral action is most probably directed against tumor products of both peptide and amine origin. These observations were recently corroborated in another patient (E.A.). After embolization this patient slowly developed an ileus due to multiple adhesions and peritoneal carcinoidosis and underwent two uneventful explorative laparotomies under combined treatment with SMS 201–995 and ketanserin. Subsequently a minor surgical revision of a cutaneous fistula was performed with sole ketanserin pretreatment. Shortly after induction of anesthesia (fentanyl 0.2 mg, midazolam 20 mg, and vecuronium 6 mg) a severe crisis reaction developed, which was reversed by acute administration SMS 201–995 IV.

In conclusion, we recommend the prophylactic use of SMS 201–995 in preparation for surgery or hepatic arterial embolization in patients with midgut carcinoid tumors. Subsequent challenge with PG should be performed in each patient to evaluate the efficacy of the pretreatment. In carcinoid patients with disseminated disease, a crisis reaction may easily develop, even during minor surgery, despite the use of anesthetics designed to avoid such a complication. It is not sufficient to antagonize only 5-HT_2 receptors, though such may be an important adjunct to therapy with SMS 201–995 in case release of 5-HT is not completely blocked by SMS 201–995. Chronic treatment with the somatostatin analogue SMS 201–995 reduces provoked release of tumor products and depress the basal levels of 5-HT. Acute IV treatment with SMS 201–995 has additional peripheral actions that may be very useful in emergency situations.

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Pharmacodynamics of Vecuronium and Atracurium in the Obese Surgical Patient

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WEINSTEIN JA, MATTEO RS, ORNSTEIN E, SCHWARTZ AE, GOLDSTOFF M, THAL G. Pharmacodynamics of vecuronium and atracurium in the obese surgical patient. Anesth Analg 1988;67:1149–53.

The effect of obesity on the duration of action of the nondepolarizing muscle relaxants atracurium and vecuronium was studied in 28 neurosurgical patients. In obese patients given vecuronium (0.1 mg/kg), the time to go from 5 to 25% of recovery of twitch response was statistically significantly longer (14.6 ± 7 minutes, mean ± SD) than it was in nonobese control patients (6.9 ± 2 minutes). Similarly, with vecuronium times for recovery from 25 to 75% were longer (33 ± 15 minutes) in obese patients than in control patients (13.2 ± 2 minutes), as was time to 75% recovery, 82 ± 30 minutes in obese patients, 50 ± 9 minutes in controls. In contrast, obese patients given atracurium (0.5 mg/kg) exhibited no difference in recovery indexes or recovery times when compared to control patients of normal weight. The prolonged duration of action of vecuronium in obese patients is most likely related to impaired hepatic clearance and/or an overdose effect with recovery occurring during the distribution phase. That the duration of action of atracurium is not prolonged in the obese is believed due to this relaxant's not depending on organ function for elimination.

Key Words: NEUROMUSCULAR RELAXANTS—vecuronium, atracurium. PHARMACODYNAMICS—vecuronium, atracurium. COMPLICATIONS—obesity.

Little is known about the effects of obesity on the pharmacodynamics of muscle relaxants. Pancuronium has been studied in the obese with conflicting results. Tsueda et al. (1) found that obese patients required significantly more pancuronium than controls for the maintenance of 90% paralysis throughout surgery. After correcting for body surface area (BSA), however, there was no difference in pancuronium requirements between the two groups. Feingold (2) reanalyzed the data of Tseuda et al. and found that the cumulative dose of pancuronium strongly correlated with the square root of elapsed time. Thus, Feingold recommends that the initial and repeat doses of pancuronium be determined from previously derived tables rather than calculations based on BSA. Soderberg et al. (3), on the other hand, found that the total required dosage of pancuronium (per hour) in the obese was the same as for normal patients. Therefore, they recommended, muscle relaxant dosage should be based on ideal body weight (IBW).

More recently, prolonged action and elimination of metocurine has been documented in obese patients (4). Decreased urinary excretion of metocurine in the obese was suggested as a possible mechanism for this prolongation.

The purpose of this study was to see if vecuronium and atracurium, muscle relaxants eliminated primarily by nonrenal routes (5,6) also have prolonged duration of action in obese surgical patients.

Methods

Following institutional review board approval, informed consent was obtained from all patients. Fourteen obese patients and 14 controls undergoing elective neurosurgery were studied. In the control group, operations included six lumbar laminectomies, six craniotomies, one ventriculo-peritoneal shunt, and one popliteal exploration. In the obese group, there

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Table 1. Demographics and Intraoperative Conditions (Mean ± SD)

	Vecuronium			Atracurium		
	Obese	Control	*P*	Obese	Control	*P*
%IBW[a]	139 ± 15	106 ± 6	<0.001	146 ± 3	98 ± 6	<0.001
%Fat	42 ± 8	20 ± 3	<0.01	41 ± 6	19 ± 6	<0.001
Age (yr)	53 ± 6	42 ± 15	0.11	52 ± 12	28 ± 7	<0.01
Sex (F:M)	4:2	4:2	1	6:0	5:1	0.3
Temp. (°C)	35.7 ± 0.4	35.4 ± 0.7	0.4	35.4 ± 0.9	35.7 ± 0.6	0.5
$Etco_2$	29 ± 4	30 ± 2	0.8	30 ± 2	29 ± 4	0.8

[a]IBW: Ideal body weight based on formula of the Metropolitan Life Insurance Co. (7).

were seven lumbar laminectomies, two cervical laminectomies, three craniotomies, one transphenoidal adenectomy, and one ventriculo-peritoneal shunt. Obese patients were at least 130% of ideal body weight (IBW) based on the formula of the Metropolitan Life Insurance Co. (7): IBW (males) = 110 lb + 5 lb/inch above or below 5 feet height; IBW (females) = 100 lb + 5 lb/inch above or below 5 feet height.

The percent of the patient's body weight consisting of fat (% fat) was calculated by the method of Weisberg (8) and Gubner (9):

$$\% \text{ fat} = 90 - 2 \text{ (height} - \text{abdominal girth in inches)}$$

Patients were excluded from the study if they had cardiac, hepatic, renal, or neuromuscular disease, or if they were taking medication known to affect neuromuscular function. Seven obese patients and seven controls received atracurium. Vecuronium was given to the other seven obese and seven control patients. The sex distribution was the same in the obese and control groups. In the vecuronium study, there was no statistical difference in the ages of the obese and control patients. Because age does not affect atracurium dynamics in adults (10), it was not controlled in the atracurium portion of the study.

Anesthesia was induced with thiopental 4–14 mg/kg, N_2O, O_2 and halothane 1–2%. Maintenance of anesthesia was with 60% N_2O, 40% O_2, and 1% halothane (inspired concentration). The ulnar nerve was stimulated at the wrist, with a supramaximal stimulus of 0.2-msec duration at 0.1 Hz from a Grass Model S-44 used in conjunction with a stimulus isolation unit. The response was measured with a Grass force-displacement transducer, Model FT-10 applied to the thumb. After a control twitch height was established, the patients received either 0.1 mg/kg of vecuronium or 0.5 mg/kg of atracurium IV bolus. End-tidal CO_2 ($Etco_2$) was kept between 25–35 mmHg. An esophageal temperature between 34.5 and 36.6°C was maintained with warming blankets. $Etco_2$ and temperature did not differ significantly between groups.

The times to 5, 25, 50, 75, and 100% recovery of twitch response were recorded for each patient. From these data the times to go from 5% to 25% and 25% to 75% of recovery of twitch response (recovery indexes) were calculated. Recovery times and indexes were compared between the obese and control groups using two-tailed Student's *t*-test. The groups' characteristics and intraoperative conditions were similarly compared. The male:female breakdown was compared using χ^2. Percent fat and percent of ideal body weight (% IBW) were correlated with recovery indexes and times by linear regression. The threshold for statistical significance was $P < 0.05$.

Results

The demographic characteristics of the groups and the intraoperative conditions are summarized in Table 1. In terms of absolute weight, obese patients averaged 80 kg with a range of 61–95 kg and the controls averaged 60 kg, with a range of 48–77 kg.

As shown in Table 2, obese patients receiving vecuronium had significantly prolonged 5–25% and 25–75% recovery indexes. The time to 75% recovery was also significantly prolonged in obese patients given vecuronium. Consequently, the regression of % IBW to 25–75% recovery ($r = 0.81$, $P < 0.005$) was significant for vecuronium (Table 3). The regression of % fat to 25–75% recovery, however, was more closely correlated ($r = 0.91$, P 0.005). The regression of % IBW to 5–25% recovery was weakly correlated ($r = 0.61$, P 0.05). The regressions of both % IBW to time for 75% recovery (T 75%) and % fat to T 75% were significant. Multiple regression on age and % IBW compared to 25–75% recovery showed that age was not significantly related to recovery in this study ($P = 0.97$). The recovery index (25–75%) of patients receiving vecuronium increased 0.6 min for each percent increase in weight over the IBW (Fig. 1). Even more significantly, in these patients as the % fat increases 1% the 25–75% recovery is prolonged 1.1 min. The predicted 5–25% and 25–75% recovery in-

Table 2. Recovery Indexes and Recovery Times (Mean ± SD)

	Vecuronium			Atracurium		
	Obese	Control	*P*	Obese	Control	*P*
5–25% (min)	14.6 ± 6.7	6.9 ± 1.9	<0.05	10.9 ± 3.9	10.6 ± 2.7	NS
25–75% (min)	33.0 ± 15.0	13.2 ± 1.9	<0.01	9.7 ± 4.1	9.3 ± 2.6	NS
Time 50% (min)	63.5 ± 23.1	42.5 ± 8.5	NS	48.6 ± 6.8	47.3 ± 10.4	NS
Time 75% (min)	82.2 ± 29.9	50.0 ± 8.5	<0.05	54.3 ± 7.4	52.6 ± 11.5	NS
Time 100% (min)	143.4 ± 53.0	86.4 ± 37.9	NS	67.7 ± 7.5	68.2 ± 23.7	NS

NS, not significant

Table 3. Regressions: Obesity and Recovery Times

	Vecuronium		Atracurium	
X:Y	*r*	*P*	*r*	*P*
%Fat:25–75%	0.91	<0.005	0.09	NS
%IBW:25–75%	0.81	<0.005	0.06	NS
%Fat:5–25%	0.78	NS	0.17	NS
%IBW:5–25%	0.61	<0.05	0.13	NS
%Fat:T 75%	0.80	<0.05	0.01	NS
%IBW:T 75%	0.61	<0.05	0.02	NS

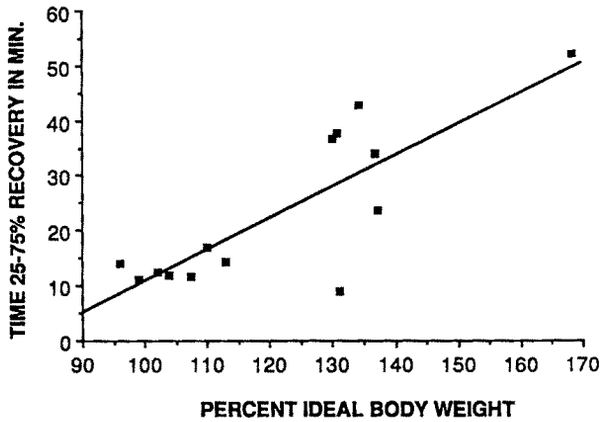

Figure 1. Vecuronium (0.1 mg/kg). Regression line relating time of 25–75% recovery of twitch to ideal body weight, $r = 0.81$.

dexes, together with the predicted time to 75% recovery for obese patients receiving vecuronium, are listed in Table 4. In contrast with atracurium, there were no changes in its recovery times or recovery indexes in the obese patients. Regressions of % IBW (Fig. 2) and % fat to recovery indexes showed no relationship in patients receiving atracurium.

Discussion

Obese patients have a prolonged recovery from neuromuscular blockade when vecuronium but not atracurium, is given. In addition, atracurium is associated with a consistent recovery time in both normal and

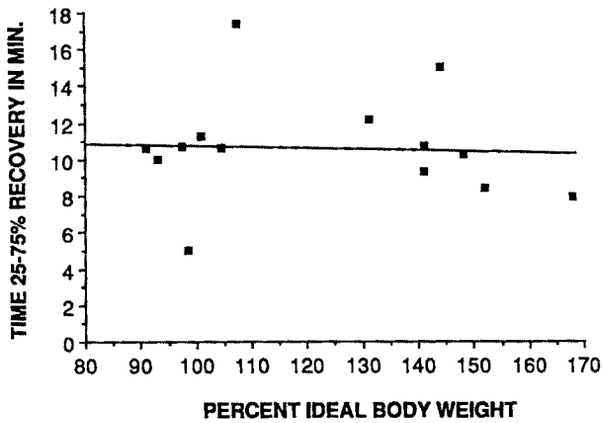

Figure 2. Atracurium (0.5 mg/kg). Regression line relating time of 25–75% recovery of twitch to ideal body weight, $r = 0.06$.

obese patients with little variability within groups. On the other hand, with vecuronium the prolonged action in the obese was associated with large individual variability. In the obese, the standard deviation for the recovery index for vecuronium was 15 minutes but for atracurium it was only 4 minutes.

Possible explanations for the observed differences between atracurium and vecuronium in the obese could be (i) the increased sensitivity of the neuromuscular junction to vecuronium in the obese, (ii) the delayed elimination of vecuronium in the obese, or (iii) the differing effects of a relative overdosage for the two drugs. A previous study of metocurine in the obese showed no difference in the plasma concentration-response relationship (4), and so delayed elimination seems to be the more likely explanation. The fact that obesity does not alter the recovery from neuromuscular blockade with atracurium is most likely because this relaxant does not depend on organ function for elimination.

The elimination of vecuronium, in contrast, is highly dependent on hepatic clearance. Forty percent of vecuronium is excreted unchanged in bile in the first 24 hours (5).

Occult abnormal liver histopathology has been documented in the obese despite normal liver function tests. Galambos and Wills (11) found that 80% of

Table 4. Predicted Recovery Times in Obese Patients

	Normal	Obese	
	100% IBW	130% IBW	160% IBW
25–75% (min)	13	31	49
5–25% (min)	7	12	18
75% (min)	50	74	98

obese patients undergoing jejunoileal bypass had at least one of four types of hepatic histological abnormalities: lobular hepatitis, fibrosis, portal hepatitis, or steatosis. As many as 26% of the patients with abnormalities on biopsy had normal preoperative liver function tests (SGOT, bilirubin, albumin, and alkaline phosphatase). In a review of the subject, Andersen and Gluud (12) reported abnormal liver biopsies in 88% of obese patients. And in their own series of obese patients, Andersen et al. (13) found a 93% incidence of abnormal liver biopsies. The liver function tests were not significantly different in obese patients with normal and abnormal biopsies. Liver disease has been shown to prolong neuromuscular blockade induced by vecuronium (14).

In addition to abnormal liver histopathology, obese patients may have altered liver blood flow. To estimate hepatic blood flow in the obese, Alexander et al. (15) measured splanchnic blood flow using sulfobromophthalein extraction. While absolute hepatic blood flow as the fraction of total cardial output was increased in the obese, absolute levels of hepatic blood flow were slightly reduced. If hepatic blood flow were divided by body weight, the obese patients would have approximately half of the predicted normal flow. Therefore, delayed elimination of vecuronium in the obese could be due to either occult intrinsic hepatic abnormalities or relatively decreased liver blood flow.

The final possible mechanism for prolonged action of vecuronium in the obese is the effect of overdosage. Feldman and Liban (16) gave large initial bolus doses of vecuronium to healthy patients and monitored recovery times. They found that as they incrementally increased the initial bolus from 0.1 to 0.25 μg/kg, the times to 10% recovery as well as the recovery index were both incrementally prolonged. Fisher and Rosen (17) also compared recovery times with different doses of vecuronium and atracurium. They found that doubling the initial bolus prolonged both the 5–25% and 25–75% recovery times for vecuronium but not atracurium.

The most likely explanations for the prolonged recovery times when an initial bolus of vecuronium is doubled are either that recovery occurred during the elimination phase instead of the redistribution phase in the overdosed patients, or that the pharmacokinetics changed with larger doses. Fisher and Rosen (17) used computer-generated pharmacokinetic and pharmacodynamic models to explain the difference in recovery times between vecuronium and atracurium. With a small dose of vecuronium, recovery occurs during the redistribution phase. In contrast, when a large dose of vecuronium is given, recovery occurs during the elimination phase, i.e., when plasma concentration is decreasing more slowly. Atracurium differs from vecuronium in that recovery from both small and large doses occurs during the elimination phase. In this analysis, Fisher and Rosen assumed that the pharmacokinetics of the muscle relaxants were independent of the size of the dose administered.

The pharmacokinetics of different doses of vecuronium have been studied by Fahey et al. (18), Cronnelly et al. (19), and Lebrault et al. (14). Fahey et al. used a dose of 0.28 mg/kg in normal patients and 0.14 mg/kg in patients in renal failure and found no difference in pharmacokinetics, the elimination half-lives being 80 and 97 min, respectively. Cronnelly et al. gave an infusion of 0.025–0.050 mg/kg to healthy patients and found a half-life of elimination of 71 min. Lebrault et al. using a bolus dose of vecuronium 0.2 mg/kg, found the elimination half-life in healthy patients to be 58 min. The volume of distribution, steady state, in the three above-mentioned studies ranged between 194 and 270 $ml \cdot kg^{-1}$.

These studies suggest that the pharmacokinetics of vecuronium are similar over a wide range of doses.

Therefore, the mechanism for the delayed recovery from vecuronium in the obese demonstrated by this study is likely to be impaired hepatic clearance and/or an overdose effect with recovery occurring in the redistribution phase. The pharmacokinetics of vecuronium in the obese need to be studied to clarify this issue.

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Sixty-Five Years Ago In

Anesthesia & Analgesia

E. H. Williams: Nitrous Oxid (sic)-Oxygen Under Positive Pressure in Thoracic Surgery. Current Researches in Anesthesia and Analgesia: 1923;2:23–39

This paper provides fascinating insight into the anesthetic management of patients in the very early days of thoracic surgery. The basic principle was "keep it simple"—simple to an extent that would likely depolarize any modern anesthesiologist. The author prefaces this description of her experience in 21 cases of positive pressure nitrous oxide-oxygen anesthesia by disabusing the reader of any idea that the differential pressure cabinets recently developed by Willey Meyer in Europe to keep the lungs inflated when the chest was open (itself an historically most interesting aspect of anesthesia and surgery for thoracic cases) were worth anything. They were, she says, too clumsy. They were too complex. They were not practical. Also, she emphasizes, the cabinets mean that tracheal intubation was necessary. This was just too much. After all, Gwathmey had declared only three years earlier that tracheal intubation had been "largely eliminated" from clinical practice. Tracheal intubation was unnecessary. It was dangerous. So, what Dr. Williams did was simply to use an anesthesia face mask with what amounted to a simple flap-type nonrebreathing valve built into it. The mask was left on the patient's face (no tracheal tube) and the lungs were rhythmically inflated with positive pressure from N_2O-O_2 tanks without reducing valves by closing the expiratory valve on the face mask with her finger. Remove the finger and the lungs deflated. Nitrous oxide (concentrations unstated) was used because it did not injure the lungs (the way ether did). No other drugs were needed; no other drugs were used. Operations included thoracic esophagectomies for carcinoma. No deaths occurred—in the operating room.

Pharmacokinetics of Lidocaine in Nonpregnant and Pregnant Ewes

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SANTOS AC, PEDERSEN H, MORISHIMA HO, FINSTER M, ARTHUR GR, COVINO BG. Pharmacokinetics of lidocaine in nonpregnant and pregnant ewes. Anesth Analg 1988;67:1154–8.

The pharmacokinetics of lidocaine were studied in nonpregnant and pregnant ewes. The maternal femoral vessels were cannulated and, on the day of study, the urinary bladder was catheterized. Lidocaine HCl, 4–5 mg/kg, was administered by IV injection over 60 seconds. Serial samples of arterial blood and urine were collected over 4 hours, and drug concentrations were determined using a gas chromatographic technique. The volume of the central compartment was greater in pregnant than in nonpregnant ewes (1.51 ± 0.20 vs. 0.96 ± 0.16 L/kg) as was the volume of distribution at steady state (Vd_{ss}): 3.24 ± 0.40 vs. 1.78 ± 0.32 L/kg. The volume of distribution during the terminal exponential phase of drug elimination ($Vd\beta$) and total clearance of lidocaine (Cl) were also higher in pregnant animals: 4.17 ± 0.50 L/kg and 99.6 ± 8.5 $ml \cdot min^{-1} \cdot kg^{-1}$, respectively; compared to 2.46 ± 0.48 L/kg and 44.1 ± 6.5 $ml \cdot min^{-1} \cdot kg^{-1}$, in nonpregnant ewes. However, the balance between these changes in $Vd\beta$ and Cl did not result in a significant difference in the elimination half-life of lidocaine (38.1 ± 2.1 minutes in nonpregnant and 31.9 ± 3.0 minutes in pregnant ewes). If these data are applicable to humans, the risk of drug accumulation after repeated administration of lidocaine is no greater in pregnant than in nonpregnant patients.

Key Words: ANESTHETICS, LOCAL—lidocaine. PHARMACOKINETICS—lidocaine. PREGNANCY, PHARMACOKINETICS—lidocaine. ANESTHESIA—obstetrical.

Physiologic changes during pregnancy, particularly those affecting plasma volume, hematocrit, and protein concentrations, as well as alterations in cardiac output and its distribution, should alter the pharmacokinetics of drugs. There are relatively few studies addressing this issue and some of the data are contradictory. For example, in the case of meperidine, one investigation (1) showed that the initial dilution volume, the volume of distribution at steady state, and the volume of distribution during the drug elimination phase, were less in pregnant patients than in nonpregnant ones. More recently it was found that the volume of distribution and clearance of the drug were similar in parturients and nonpregnant women (2). Administration of thiopental to pregnant and nonpregnant women resulted in a longer elimination half-life in the pregnant group (3). This difference was attributed to a three-fold increase in the volume of distribution at steady state noted in pregnant patients. In addition, clearance of thiopental was significantly greater in pregnant patients, 0.29 L/min, versus 0.15 L/min in nonpregnant women. The present study was undertaken to examine the effects of gestation on the pharmacokinetics of lidocaine, a commonly used agent for regional anesthesia in surgery and obstetrics.

Materials and Methods

Six nonpregnant and ten pregnant ewes (gestational age >115 days) were used, under a protocol conforming to the institutional guidelines for animal investigation. Surgical preparation was carried out at least 4–5 days before the experiments. All ewes were deprived of food, but not water, for 24 hours before surgery. Under spinal anesthesia induced with tetracaine hydrochloride 10–12 mg, a maternal femoral artery and vein were cannulated with polyethylene

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Table 1. Heart Rate, Mean Arterial Blood Pressure, pH, and Blood Gas Tensions in Nonpregnant and Pregnant Ewes Before and at the End of Experiment

	Heart rate (beats/min)	Mean arterial pressure (mm Hg)	pH	$Paco_2$ (mm Hg)	Pao_2 (mm Hg)
Nonpregnant					
Control	112 ± 6	92 ± 6	7.43 ± 0.02	31 ± 3	96 ± 3
End of experiment	108 ± 5	90 ± 9	7.48 ± 0.01	32 ± 2	91 ± 2
Pregnant					
Control	112 ± 6	87 ± 4	7.51 ± 0.02	30 ± 2	107 ± 5
End of experiment	103 ± 6	83 ± 4	7.50 ± 0.01	31 ± 1	105 ± 4

*Values are means ± SE.

catheters, using aseptic technique. Catheters were tunnelled subcutaneously, and exteriorized within a pouch attached to the ewe's flank.

On the day of study, the ewe was contained in a cart, at liberty to stand or lie down. Food and water were provided freely. During a control period of 30 minutes, and at intervals thereafter, arterial blood samples were obtained for determination of pH and blood gas tensions. Urine was collected through a Foley catheter inserted on that morning. Lidocaine hydrochloride 5 mg/kg was then injected intravenously over 60 seconds. Less than a full dose was given if early signs of lidocaine toxicity developed. Arterial blood pressure was measured with a Statham transducer, and heart rate with a cardiotachometer. These were recorded continuously throughout the experiment.

Arterial blood samples were obtained in heparinized syringes before, and at the following intervals after the end of injection: 1, 2, 5, 10, 15, 30, 60, 90, 120, 180, and 240 minutes. Urine samples were collected, simultaneously with blood samples, beginning at 15 minutes, for volume and pH determination. Blood samples were centrifuged and plasma was separated. Urine and plasma samples were frozen until analyzed for lidocaine concentrations, using a gas chromatographic technique similar to that described by Tucker (4). The assay was calibrated to measure concentrations down to 0.05 μg/ml. The day-to-day coefficient of variation of this assay in our laboratory is <10% over the concentration range studied.

A two-compartment open model was used to describe the resulting concentration data. Initial estimates of β (elimination rate constant) were determined by linear regression analysis and, using the method of residuals (5), values for α (distribution rate constant) were derived. Using standard equations (6), initial estimates of central compartment volume of distribution (V_c) and intercompartmental rate constants (k_{12}, k_{21}, k_{10}) were determined. Using these initial estimates, pharmacokinetic data were generated by computer using a program utilizing an opportunistic, nonlinear regression method based on the algorithm of Nelder and Mead (7) (SIMPLEX). Data points were weighted according to the method of Ottaway (8), which produced greater weighting to the lower concentrations during the elimination phase of drug. The administration of lidocaine was regarded as an IV bolus injection for the purposes of pharmacokinetic analysis, because derivation of pharmacokinetic values based on a 60-second intravenous infusion resulted in data virtually identical to those obtained by calculation based on an IV bolus.

Differences in derived pharmacokinetic indices and urinary excretion of lidocaine between nonpregnant and pregnant ewes were compared using Student's t-test for unpaired values. $P < 0.05$ was considered statistically significant. Results are expressed as mean ± SE.

Results

The weights of the ewes were similar: 52.4 ± 6.8 kg in the nonpregnant group, and 54.9 ± 2.3 kg in the pregnant group. The mean gestational age of the pregnant ewes at the time of study was 125.4 ± 2.3 days, term being 148 days. The mean dose of lidocaine given was 4.99 ± 0.01 mg/kg in the nonpregnant ewes and 4.3 ± 0.2 mg/kg in the pregnant ones. In seven pregnant ewes, signs of lidocaine toxicity developed after approximately 50 seconds, and the infusion was discontinued before the full dose could be administered.

Before lidocaine injection, the heart rate, mean arterial blood pressure, arterial pH, and blood gas tensions were normal for our laboratory (9) and, in nonpregnant ewes, remained so throughout the experiment (Table 1). In pregnant ewes, injection of lidocaine resulted in a brief period of muscle rigidity, accompanied by an increase in heart rate (from 112 ± 6 to 133 ± 4 beats/min), and mean blood pressure (from 87 ± 4 to 103 ± 7 mm Hg). These drug effects subsided within 3–5 minutes.

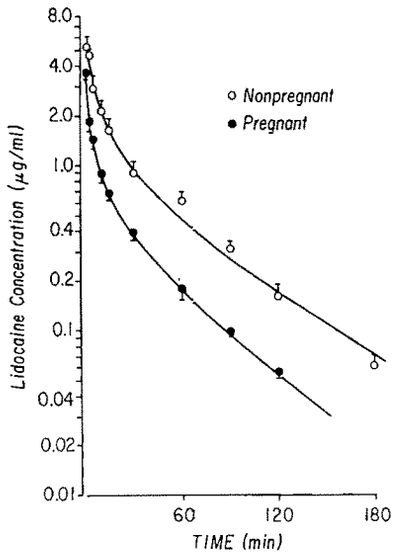

Figure 1. Plasma concentrations of lidocaine in nonpregnant and pregnant ewes (mean ± SE).

Table 2. Derived Pharmacokinetic Values

	Nonpregnant	Pregnant	*P* Value
$T_{1/2}\alpha$ (min)	4.5 ± 0.5	3.5 ± 0.5	NS
$T_{1/2}\beta$ (min)	38.1 ± 2.1	31.9 ± 3.0	NS
Vc (L/kg)	0.96 ± 0.16	1.51 ± 0.20*	<0.05
Vd_{ss} (L/kg)	1.88 ± 0.32	3.24 ± 0.40*	<0.01
$Vd\beta$ (L/kg)	2.46 ± 0.48	4.17 ± 0.50*	<0.01
Cl ($ml \cdot min^{-1} \cdot kg-1$)	44.1 ± 6.5	99.6 ± 8.5*	<0.001
K_{12}	0.068 ± 0.015	0.107 ± 0.024	NS
K_{21}	0.065 ± 0.010	0.089 ± 0.019	NS
K_{10}	0.049 ± 0.005	0.067 ± 0.004*	<0.01

*Significantly different from nonpregnant.
Values are means ± SE.

The highest plasma concentrations of lidocaine were measured in samples drawn at 1 minute; these were 5.12 ± 0.92 μg/ml in the nonpregnant, and 3.66 ± 0.29 μg/ml in the pregnant group (Fig. 1). The subsequent decay in plasma lidocaine concentrations was biexponential in both groups. In only three pregnant ewes were lidocaine concentrations measurable in samples obtained beyond 120 minutes, whereas in the nonpregnant ewes they were measurable up to 180 minutes.

Derived pharmacokinetic indices are listed in Table 2. The distribution half-life was similar in both groups, being 4.5 ± 0.5 minutes in the nonpregnant and 3.5 ± 0.5 minutes in the pregnant. The elimination half-lives were also similar: 38.1 ± 2.1 and 31.9 ± 3.0 minutes in the nonpregnant and pregnant ewes, respectively. The volume of the central compartment was higher in pregnant ewes (1.51 ± 0.20 L/kg, compared to 0.96 ± 0.16 L/kg in the nonpregnant ones). The pregnant ewes had a significantly larger volume of distribution at steady state (Vd_{ss}) and during the drug elimination phase ($Vd\beta$); 3.24 ± 0.40 and 4.17 ± 0.50 L/kg, versus 1.88 ± 0.32 and 2.46 ± 0.48 L/kg, respectively, in the nonpregnant animals. The total body clearance of lidocaine was also greater in pregnant ewes, 99.6 ± 8.5, compared to 44.1 ± 6.5 $ml \cdot min^{-1} \cdot kg^{-1}$ in nonpregnant animals.

Table 3. Total Urinary Excretion of Lidocaine

	Total lidocaine excretion	
pH Group	μg kg	% of Administered dose
Nonpregnant	96.9 ± 35.0	1.5 ± 0.5
Pregnant	77.6 ± 28.7	1.9 ± 0.7

Values are means ± SE

Table 4. Total Excretion of Lidocaine in Relation to Urine pH

	Total excretion	
pH Group	(μg kg)	% of administered dose
Nonpregnant		
low	169.8 ± 26.3*	2.5 ± 0.6*
high	24.7 ± 10.7	0.4 ± 0.2
Pregnant		
low	127.9 ± 39.2*	2.7 ± 0.8*
high	17.2 ± 3.5	0.4 ± 0.1

*Significantly different from corresponding high pH group.
Values are means ± SE.

There was considerable variability in urinary excretion of lidocaine (Table 3). When each group was divided according to the urine pH (low pH, 5.2–7.2, and high pH, 7.3–9.0), it was found that in nonpregnant, as well as in pregnant ewes, the total excretion of lidocaine was greater in animals having more acidic urine (Table 4).

Discussion

It is apparent that gestation has an effect on the pharmacokinetics of lidocaine after intravenous administration. The volumes of distribution at steady state (Vd_{ss}) and with respect to the elimination phase ($Vd\beta$), as well as the total clearance (Cl) were significantly greater in pregnant than in the nonpregnant ewes. The balance between the volume of distribution and clearance was such that the elimination half life was similar in both groups of animals.

The volume of the central compartment (V_c) in the nonpregnant ewe, 0.96 ± 0.16 L/kg^{-1}, is in agreement with the data obtained in our earlier study (9)

comparing the ovine pharmacokinetics of lidocaine in the nonpregnant adult, newborn, and fetus. In pregnant animals, V_c, Vd_{ss}, and $Vd\beta$ were significantly greater. Pregnancy-related increases in these indexes have also been reported by others (10). There may be several reasons for this. Pregnancy is associated with a marked increase in cardiac output and redistribution of blood flow to many organs (11). There is also a marked increase in blood volume and extravascular water content (12,13). Decreases in plasma albumin and α_1-acid glycoprotein concentrations during pregnancy will increase the unbound fraction of drug available for tissue distribution (14,15). Placental transfer itself should contribute to increases in the volume of distribution of maternally administered drug. This is particularly important for weak bases such as amide local anesthetics, which tend to accumulate in the more acidic fetal environment through the ion-trapping mechanism (16).

In contrast to a published report (10), in this study the total clearance of lidocaine was significantly greater in pregnant than in nonpregnant animals. Because the clearance of lidocaine is mostly by flow-dependent hepatic metabolism (17), this increase in Cl may in part be due to enhanced hepatic blood flow, which has been reported as 55 $ml \cdot min^{-1} \cdot kg^{-1}$ in nonpregnant and 65 $ml \cdot min^{-1} \cdot kg^{-1}$ in pregnant, nonfasted sheep (18). Individual values for pregnant sheep were as high as 110 $ml \cdot min^{-1} \cdot kg^{-1}$. In another study, in which we administered lidocaine to pregnant sheep, by constant-rate intravenous infusion over a period of 180 minutes to achieve steady-state plasma drug concentrations, clearance was approximately 50 $ml \cdot kg^{-1} \cdot min^{-1}$ (19). The difference between clearance values obtained with a bolus injection and with a constant rate infusion may be attributed to the fact that prolonged infusion of lidocaine alters hepatic blood flow and drug extraction (20). In a study using nonpregnant sheep, Mather et al. (17) found that hepatic and renal clearances could not account for the total body clearance of lidocaine. The lung and gut were not involved and, in a different study by the same group, the hind-quarters of the sheep were implicated in extra hepatic clearance (21). If this site were more important during ovine pregnancy, possibly due to increased cardiac output and changes in lidocaine distribution, then this would also account, in part, for the greater total body clearance in pregnant sheep observed in the current study. The fetus is capable of metabolizing lidocaine and also of excreting unchanged lidocaine in its urine (9,22), and thus is contributing to the maternal clearance of the drug.

There was no difference detected in the total amount of lidocaine excreted in the urine between pregnant and nonpregnant ewes. In both groups, larger amounts of the drug were excreted in acidic than in more alkaline urine. This finding is in agreement with that in humans, in whom the renal clearance of local anesthetics was increased by acidification of urine (23). When total renal excretion of unchanged lidocaine was expressed as a proportion of the injected dose, it did not exceed 3%.

Pregnant ewes were less tolerant of lidocaine infusion, which is in keeping with other observations of enhanced local anesthetic tissue penetration and toxicity in pregnancy (24,25). This may be related to the decreased plasma protein binding of local anesthetics in pregnant animals and, possibly, to enhanced cardiac output.

In conclusion, our data indicate that pregnancy alters the pharmacokinetics of lidocaine. However, the interplay between the changes in $Vd\beta$ and Cl was such that the elimination half life was not affected. If these findings are applicable to humans, pregnant women should not be at a greater risk of drug accumulation after repeated injections, compared to nonpregnant patients. However, they may be at greater risk of toxicity after an unintended intravascular injection of drug.

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Epidural Morphine Delivered by a Percutaneous Epidural Catheter for Outpatient Treatment of Cancer Pain

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DOWNING JE, BUSCH EH, STEDMAN PM. Epidural morphine delivered by a percutaneous epidural catheter for outpatient treatment of cancer pain. Anesth Analg 1988;67:1159–61.

Twenty-three outpatients with cancer pain refractory to other methods of pain control were treated with epidural morphine (EM) delivered through a chronically placed percutaneous lumbar epidural catheter. Patients and their families were taught to administer EM at home. Mean EM doses ranged from 18 to 31 mg/day. Mean catheter lifespan was 6.3 weeks. There were no catheter-related infections or cases of respiratory depression. After 2500 patient treatment days, we have found this method to be a safe and effective method of cancer pain management in outpatients.

Key Words: ANALGESICS—morphine. ANESTHETIC TECHNIQUES, EPIDURAL—morphine. PAIN, CHRONIC.

As modern methods of cancer therapy and palliation have developed, the number of patients living for months, and sometimes years, with severe malignant pain has increased. Control of chronic pain with oral analgesics becomes difficult because of inadequate analgesia and unacceptable sedation. An alternative to oral narcotics is epidurally administered morphine sulfate (EM) (1–6).

We have reviewed the cases of 23 ambulatory patients with chronic cancer pain treated as outpatients with EM via a percutaneously placed catheter. Patients and family members were taught to administer EM and to care for the catheter at home for periods as long as 58 weeks. Although we were concerned about respiratory depression and catheter infection, no serious side effects or complications developed in our 2500 patient days of use.

We report our technique of epidural catheter placement, average EM doses, average catheter lifespan, and rationale for catheter changes.

Materials and Methods

Patients with pain of malignant origin were referred by their physician because of inadequate analgesia with oral or parenteral analgesics and failure to control pain with radiation therapy or palliative surgical procedures. Epidural pain control was discussed with the patient and family members. If families were willing to accept responsibility for home catheter care and EM administration, the patient was offered EM therapy. Informed consent was obtained.

All patients were hospitalized for initiation of EM therapy. Lumbar approach to the epidural space was used regardless of the location of pain. Catheters were threaded 10 to 15 cm in a cephalad direction to reduce the risk of accidental catheter displacement and to allow deliberate partial withdrawal of a catheter if injection through it became difficult. We employed a multiple orifice, bullet tip catheter (Product #CE18TK, Burron Medical Inc., Bethlehem, PA) to minimize the risk of catheter outflow obstruction.

After catheter placement, the skin was treated with an adhesive skin preparation (Skin Prep®, Pfizer Group, Largo, FL), a sterile 5 × 5 cm gauze was placed over the skin entrance site, and a large transparent dressing (Tegaderm®, 3M, St. Paul, MN) was applied. The catheter was fitted with a 0.22-μm filter (Product #4980, Concord Labs, Keene, NH) and an injection port. All patients received preservative-free morphine sulfate in sterile saline from 10-ml single dose ampules at a concentration of 0.1% (Duramorph®, A. H. Robins Co., Richmond, VA). Initially, 5 mg was injected every 12 hours. Then, over several days, oral and parenteral narcotic intake was

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Table 1. Patient Summary

Age	Sex	Cancer	Pain location	Total duration of EM[a] (weeks)	Why EM discontinued	Adjunctive nonepidural medications
71	F	Unknown 1°	Ribs/flank	15	Expired	MS[b] Contin®
46	M	Lung	Flank/hip	27	Expired	MS Contin®
51	M	Lung	Chest/flank	58.5	Expired	None
74	M	Colon	Hip/leg	27	Expired	Methadone
39	F	Anus	Buttocks/leg	26	Remission	Hydromorphone
39[c]	F	Anus	Buttocks/leg	14	Expired	Hydromorphone
52	M	Lung	Chest/arm	7	Expired	MS Contin®
45	M	Unknown 1°	Pelvis	17.5	Expired	MS Contin®
71	M	Prostate	Back	11	Expired	None
60	M	Melanoma	Hip/leg	4	Expired	Methadone
55	M	Renal cell	Back	18.5	Expired	Hydromorphone
62	F	Pancreas	Back	6	Expired	Methadone
70	M	Colon	Back/pelvis	20+	In progress	None
58	M	Bladder	Hip/leg	13	Expired	None
53	F	Pancreas	Back	8	Trial of infusion pump	None
53[d]	F	Pancreas	Back	10	Expired	None
72	M	Prostate	Back	7	Trial of infusion pump	MS Contin®
58	M	Pancreas	Abdomen/back	12	Expired	Methadone
64	F	Lung	Shoulder/hip	16	Expired	None
68	F	Lung	Flank	3.5	Expired	None
62	M	Prostate	Rib/hip	8.5	Spinal cord compression due to metastatic disease	None
67	M	Lung	Back/flank	4	Catheter dislodged	None
65	M	Sarcoma	Abdomen/back	8.5	Expired	Hydromorphone
65	F	Biliary tract	Hip/chest	8+	In progress	0
58	F	Lung	Rib/abdomen	5	Expired	0
				Mean = 15 weeks		

[a]EM, epidural morphine therapy.
[b]MS Contin®, morphine sulfate pentahydrate, controlled release oral tablets, Purdue Frederick Co., Norwalk, CT.
[c]After 11-month remission, cancer and pain recurred.
[d]Poor analgesia with epidural pump for 6.5 weeks; patient returned to percutaneous EM.

decreased while EM dosage was adjusted to establish a stable initial effective dose. Nonepidural narcotics were used for breakthrough pain. All patients were managed on a medical/surgical nursing floor using our standard EM observation orders (7). During the hospital phase of dosage adjustment, anesthesiology and nursing personnel instructed the patient and family in the technique of dosage administration and catheter care. Instruction was given on how to monitor respiration, recognize respiratory depression, and administer intramuscular naloxone.

After a stable initial dosage regimen was established and teaching was completed (3 to 5 days), the patients were discharged. A 2-week prescription for preservative-free morphine, written instructions, and a 24-hour phone number to call for assistance were provided. Home-healthcare nurses visited patients at least three times a week for 1 month to ensure compliance with our dosage and administration guidelines and to monitor the catheter site.

Epidural catheters were changed for several reasons. Because hospital visits often represented a hardship for our patients and their families, we replaced the catheter when the patient was at the hospital for another appointment if the catheter had been in place for 6 to 8 weeks. We felt these "prophylactic" replacements would save the patient the problem of catheter malfunction, loss of epidural access, and a return to the hospital. Other reasons for changing the catheter included difficulty in injection, leakage at the skin entrance site, and inadvertent dislodgement.

Results

Table 1 summarizes patient data and total duration of EM therapy that averaged 15 weeks. Also detailed are the reasons for eventual discontinuation of EM therapy: death in 75% of the cases. Forty-three percent of our patients were completely weaned from adjunctive narcotics.

Figure 1 shows EM doses at time of initial discharge from the hospital and the dose at the time of termination of EM therapy. These mean doses were 18 and 31 mg/day, respectively. Most patients re-

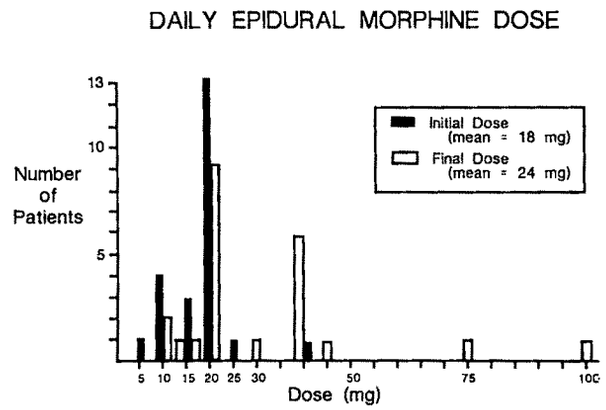

Figure 1. Mean EM dosage at initiation and termination of EM therapy.

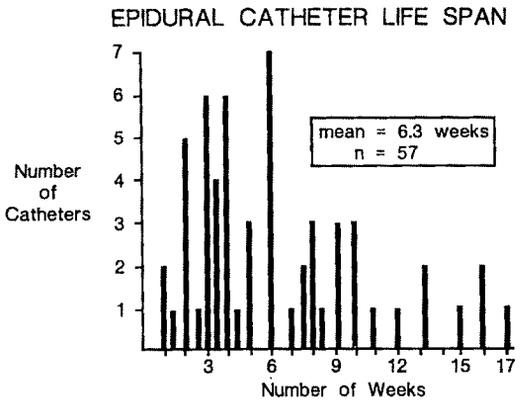

Figure 2. Epidural catheter lifespan in weeks.

quired a gradual increase in the EM dose. It is unknown whether this was due to progression of disease or tolerance to the EM.

Figure 2 illustrates catheter lifespan which averaged 6.3 weeks with a range of 1 to 17 weeks.

Also significant is that no patient in this series developed clinically evident respiratory depression, despite concommitant use of oral narcotics and high EM doses (up to 100 mg/day). There were no detected cases of catheter or epidural space infection. Also absent were pruritis and urinary retention, side-effects commonly seen in patients naïve to narcotics. All patients in this series had received narcotics before initiating EM therapy.

Discussion

Epidural morphine has been used for treating chronic cancer pain; however, some practitioners have been concerned about the risks of maintaining an epidural catheter for weeks or months because of possible side effects. We have found the use of a simple percutaneous catheter to have advantages over implantable epidural pump systems (8,9). Our technique involves no surgical procedure for placement, provides great dosage flexibility, and may well be less costly than implantable systems. We found our system is reliable and acceptable to our patients, and we have yet to encounter significant evidence of skin, epidural, or subarachnoid infection or respiratory depression. While it would be difficult to prove, we believe that EM improved the quality of analgesia in these patients; also, improved mental status and quality of life often resulted from reduced use of oral and parenteral narcotics.

In a review of 9700 patient days of EM therapy, Zenz et al. (1) reported a mean catheter life of 42 days. Our mean catheter life in a review of 2500 patient days was 44 days, with one catheter in place for 119 days. Our mean initial dose of EM was 18 mg/day and our mean final dose was 31 mg/day, while Zenz et al. reported a mean daily dose of 15.6 mg.

We feel that EM therapy via a percutaneously placed catheter with home injection is a feasible and effective method for treating cancer pain refractory to other methods of pain control. This method appears relatively free of serious side effects and may significantly improve the quality of life for these terminally ill patients.

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Difficult Laryngoscopy and Diabetes Mellitus

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The incidence of difficult laryngoscopy was determined retrospectively in 40 diabetic patients having pancreas transplantations and in 75 diabetic and 112 nondiabetic patients having kidney transplantations. Diabetes was associated with a significant increase in the proportion of patients having difficult laryngoscopies in patients having renal transplants: 0.027 in patients without diabetes; 0.320 in patients with diabetes. The incidence of difficult laryngoscopy in diabetic recipients of cadaveric kidneys (0.419) was not significantly different from that in diabetic recipients of pancreas transplants (0.40), but significantly higher than that in diabetics given kidneys from living donors (0.187). Although cadaveric recipients were older than recipients of kidneys from living donors (40.8 v. 31.6 years), age at the time of transplantation was not a significant predictor of difficulty in laryngoscopy. Groups were otherwise matched for clinical, morphologic, hematologic, and biochemical indices. Diabetic stiff joint syndrome (SJS), which predisposes a subset of Type I diabetic patients to rapidly progressive microvascular disease and subsequent need for renal and/or pancreas transplantation, may lead to difficult laryngoscopy because of involvement of the atlanto-occipital joint.

Key Words: COMPLICATIONS, DIABETES—tracheal intubation. METABOLISM, DIABETES—tracheal intubation. INTUBATION, TRACHEAL—diabetes.

Anesthetic management of diabetes mellitus patients for intact pancreas transplantation led to the impression that tracheal intubation was unusually challenging in recipients. A retrospective search was conducted to determine the incidence, associated features, and possible etiology of difficult laryngoscopy in this population. Since most diabetic patients having pancreas transplantations have had previous renal transplants, groups of diabetic and nondiabetic kidney recipients were also studied.

Methods

Staff anesthesiologists reviewed the medical records of all pancreas recipients since inception of the transplant program in 1982 and of all kidney recipients in 1986. Consent to participate in a chart review was obtained in compliance with institutional Human Subjects Committee regulations, and privacy was protected by codification. Patients having two transplants within the sampled times were excluded to avoid double representation. Data were collected from the records of 40 pancreas transplantations and 187 renal transplantations. In 75 of the latter the cause of chronic renal failure was diabetes mellitus. Causes and proportions of chronic renal failure in nondiabetic recipients are listed in Table 1.

Laryngoscopy was judged "difficult" by one of 23 attending staff anesthesiologists when direct visualization of any part of the vocal cords was impossible. Laryngoscopy was considered routine when landmarks for tracheal intubation were identified on initial inspection. Details of airway evaluation and management were documented on every patient's preoperative consultation and anesthesia record, with expanded commentary when unforeseen problems arose. Notations indicating partial observation of the vocal cords (e.g., "only posterior vocal cords seen") were scored as routine for the purposes of this investigation.

In each group the frequency of difficult laryngoscopy was examined using a logit (log odds) model. The logit [logit(P) = log(P/1-P), where P is probability] of difficult laryngoscopy was modeled as a linear function of the following: the presence or absence of diabetes; whether the donor was living or cadaveric; the age, sex, height, weight, and body mass index

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Table 1. Etiology of Chronic Renal Failure in Nondiabetic Recipients of Renal Transplants (n = 112)

	Cadaver donor	Living-Related donor
Glomerulonephritis	0.15	0.22
Polycystic kidney disease	0.18	0.03
Hypertension	0.14	0.13
Alport's Syndrome	0.03	0.06
Complication of pregnancy	0.02	0.09
Other[a]	0.18	0.22
Unknown	0.30	0.25

[a]Trauma, tumor, congenital, obstructive nephropathy, and drug toxicity.

Table 2. Proportion of Difficult Laryngoscopy in Renal Transplant Recipients

	Cadaver donor (n)	Living donor (n)		Overall
Diabetic	0.419 (43)	0.188 (32)	*	0.320
Nondiabetic	0.027 (74)	0.026 (38)	NS	0.027
	*	*		*

*$P < 0.05$.

[BMI = wt(kg) ÷ ht(cm^2)] of the recipient. A likelihood ratio χ^2-test was used to detect factors with a significance level of $P < 0.05$ (1). Confidence intervals (CI) of 95% distributed as a χ^2 were calculated for significant factors in renal recipients. Mean values of blood pressure, hematocrit, hemoglobin, potassium, sodium, blood urea nitrogen (BUN), and creatinine were compared using Student's t-tests. Monthly frequency plots were constructed to detect factors varying over the sample interval.

Results

The overall proportion of difficult laryngoscopy in patients having cadaveric pancreas transplants (0.400, 95% CI: 0.267, 0.556) was not significantly different from that in diabetic patients having cadaveric kidney transplants (0.419, 95% CI: 0.282, 0.569) (Table 2). Diabetes in recipients of kidney transplants was the most important factor contributing to the over tenfold increase in likelihood of difficult laryngoscopy (0.320, 95% CI: 0.225, 0.433) compared with nondiabetic patients (0.027, 95% CI: 0.009, 0.080).

Comments in the medical records describing difficult laryngoscopy indicate that laryngeal structures were anterior to the endoscopist's line of vision, with only small portions of the posterior arytenoid cartiledges or epiglottis seen. In most instances, the tube was passed blindly into the trachea after multiple unsuccessful attempts. Three cases were complicated by laceration of the soft tissues and three by regurgitation. Three additional patients were awakened and the endotracheal tube then placed using a fiberoptic bronchoscope. Two patients required emergency tracheostomy.

Among diabetic patients receiving kidney transplants from cadavers, the frequency of difficult laryngoscopy (0.419, 95% CI: 0.282, 0.569) was more than double that seen in diabetics having kidney transplants from living donors (0.188, 95% CI: 0.087, 0.359) ($P < 0.05$) (Table 2). No differences were detected between any groups for height, weight, BMI, blood pressure, hematocrit, hemoglobin, potassium, sodium, BUN, or creatinine. The single factor discriminating cadaveric from living-related renal recipients was age at transplant: 40.8 years v. 31.6 years for diabetic patients; 44.1 years v. 32.8 years for nondiabetic patients ($P < 0.0001$). However, when entered as a continuous covariate age did not predict difficult laryngoscopy.

A significantly larger proportion of male pancreas recipients (0.542, n = 24) had difficult laryngoscopy than females (0.188, n = 16, $P < 0.05$), although sex was not a significant predictor in kidney recipients.

The incidence of difficult laryngoscopy in nondiabetic renal recipients (0.027, 95% CI: 0.009, 0.080) was greater than the overall institutional norm of 0.005. The latter figure is derived from monthly chart review of approximately 10,000 patients for each of the past 5 years.

Inspections of frequency plots revealed even distribution of difficult and nondifficult laryngoscopies over the course of the sample year with no apparent systematic fluctuations.

Discussion

Despite suspicion that pancreas transplant recipients are at risk for difficult laryngoscopy, the magnitude of the incidence was unanticipated. Corresponding results in the diabetic renal recipients were similarly unforeseen, since this group was originally chosen as a control. Methodological constraints of a retrospective search must be acknowledged, yet the large sample sizes in this investigation afford a broad base of inference, and inclusion of all available patients minimizes sampling bias. Identification of the problem (ease of laryngoscopy) and of the scored variables was explicit, and intubating conditions were judged by staff anesthesiologists. Finally, the lack of a signif-

Table 1. Etiology of Chronic Renal Failure in Nondiabetic Recipients of Renal Transplants (n = 112)

	Cadaver donor	Living-Related donor
Glomerulonephritis	0.15	0.22
Polycystic kidney disease	0.18	0.03
Hypertension	0.14	0.13
Alport's Syndrome	0.03	0.06
Complication of pregnancy	0.02	0.09
Other[a]	0.18	0.22
Unknown	0.30	0.25

[a]Trauma, tumor, congenital, obstructive nephropathy, and drug toxicity.

Table 2. Proportion of Difficult Laryngoscopy in Renal Transplant Recipients

	Cadaver donor (n)	Living donor (n)		Overall
Diabetic	0.419 (43)	0.188 (32)	*	0.320
Nondiabetic	0.027 (74)	0.026 (38)	NS	0.027
	*	*		*

*$P < 0.05$.

[BMI = wt(kg) ÷ ht(cm^2)] of the recipient. A likelihood ratio χ^2-test was used to detect factors with a significance level of $P < 0.05$ (1). Confidence intervals (CI) of 95% distributed as a χ^2 were calculated for significant factors in renal recipients. Mean values of blood pressure, hematocrit, hemoglobin, potassium, sodium, blood urea nitrogen (BUN), and creatinine were compared using Student's t-tests. Monthly frequency plots were constructed to detect factors varying over the sample interval.

Results

The overall proportion of difficult laryngoscopy in patients having cadaveric pancreas transplants (0.400, 95% CI: 0.267, 0.556) was not significantly different from that in diabetic patients having cadaveric kidney transplants (0.419, 95% CI: 0.282, 0.569) (Table 2). Diabetes in recipients of kidney transplants was the most important factor contributing to the over tenfold increase in likelihood of difficult laryngoscopy (0.320, 95% CI: 0.225, 0.433) compared with nondiabetic patients (0.027, 95% CI: 0.009, 0.080).

Comments in the medical records describing difficult laryngoscopy indicate that laryngeal structures were anterior to the endoscopist's line of vision, with only small portions of the posterior arytenoid cartiledges or epiglottis seen. In most instances, the tube was passed blindly into the trachea after multiple unsuccessful attempts. Three cases were complicated by laceration of the soft tissues and three by regurgitation. Three additional patients were awakened and the endotracheal tube then placed using a fiberoptic bronchoscope. Two patients required emergency tracheostomy.

Among diabetic patients receiving kidney transplants from cadavers, the frequency of difficult laryngoscopy (0.419, 95% CI: 0.282, 0.569) was more than double that seen in diabetics having kidney transplants from living donors (0.188, 95% CI: 0.087, 0.359) ($P < 0.05$) (Table 2). No differences were detected between any groups for height, weight, BMI, blood pressure, hematocrit, hemoglobin, potassium, sodium, BUN, or creatinine. The single factor discriminating cadaveric from living-related renal recipients was age at transplant: 40.8 years v. 31.6 years for diabetic patients; 44.1 years v. 32.8 years for nondiabetic patients ($P < 0.0001$). However, when entered as a continuous covariate age did not predict difficult laryngoscopy.

A significantly larger proportion of male pancreas recipients (0.542, n = 24) had difficult laryngoscopy than females (0.188, n = 16, $P < 0.05$), although sex was not a significant predictor in kidney recipients.

The incidence of difficult laryngoscopy in nondiabetic renal recipients (0.027, 95% CI: 0.009, 0.080) was greater than the overall institutional norm of 0.005. The latter figure is derived from monthly chart review of approximately 10,000 patients for each of the past 5 years.

Inspections of frequency plots revealed even distribution of difficult and nondifficult laryngoscopies over the course of the sample year with no apparent systematic fluctuations.

Discussion

Despite suspicion that pancreas transplant recipients are at risk for difficult laryngoscopy, the magnitude of the incidence was unanticipated. Corresponding results in the diabetic renal recipients were similarly unforeseen, since this group was originally chosen as a control. Methodological constraints of a retrospective search must be acknowledged, yet the large sample sizes in this investigation afford a broad base of inference, and inclusion of all available patients minimizes sampling bias. Identification of the problem (ease of laryngoscopy) and of the scored variables was explicit, and intubating conditions were judged by staff anesthesiologists. Finally, the lack of a signif-

icant difference between groups in hematologic, biochemical, morphologic, and clinical indices suggests the groups of patients studied were otherwise well-matched.

One case report linking unanticipated airway complications with diabetes mellitus has previously appeared (2). In this report, a candidate for kidney transplantation was described with "stiff joint syndrome" (SJS), a condition seen in Type I insulin-dependent diabetic patients in association with rapidly progressive microangiopathy, nonfamilial short stature, tight waxy skin, and limited joint mobility. The incidence of SJS in over 1500 cases of Type I diabetes in 10 published series is 33.2% (3). SJS is not associated with sex, race, severity of diabetes, or degree of control of blood glucose levels. Increasing prevalence and severity of SJS are seen in longstanding diabetes, but duration of diabetes and not age at the time of diagnosis is the responsible factor (3).

Radiologically detected inability to extend the atlanto-occipital joint was the mechanism proposed for difficult intubation in the patient cited above (2). Ranges of motion at the temporomandibular and cervical vertebral joints were normal. Bedside examination of the neck can be misleading since normal cervical mobility masks limited atlanto-occipital extension. Stiff joint syndrome (SJS) first involves the small joints of the digits and hands, and thus failure to approximate the palmar surfaces of the interphalangeal joints is highly correlated with the SJS. The "prayer sign" (Fig. 1) may be a clue to a deceptively easy laryngoscopy (Fig. 2), but cervical radiography is essential for accurate diagnosis.

It is likely that the high incidence of difficult laryngoscopy associated with diabetes reflects a disproportionate number of diabetic SJS patients undergoing transplantation, due to a three- to fourfold increased risk of early micro-vascular complications (3). The natural history of diabetes in our series follows a rather stereotyped course: onset before age 10, micro-albuminuria around age 20, and chronic renal failure (CRF) at about age 30. If a suitable living-related donor is available, transplantation is performed. If not, the patient is managed medically until a matched cadaveric kidney is procured.

The donor variable was a significant predictor of ease of laryngoscopy. No reasonable physiologic mechanism exists to explain this observation, suggesting that another variable was proxied. Stiff joint syndrome progresses during the interval from onset of CRF to cadaveric transplantation, perhaps accounting for the higher incidence of difficult laryngoscopy compared with younger recipients of living related kidneys. The absence of a donor effect among non-

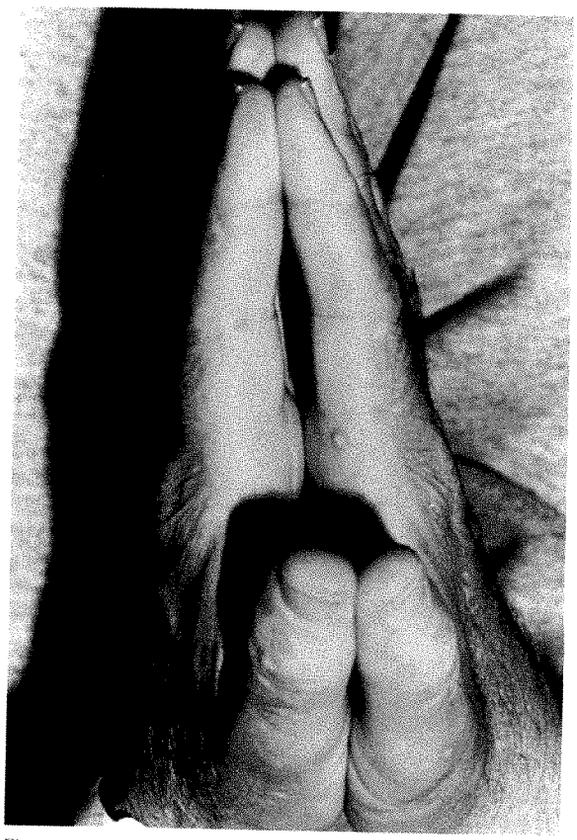

Figure 1. A renal transplant candidate with diabetes. The patient is unable to approximate the palmar surfaces of the phalangeal joints despite maximal effort (a "prayer sign"), secondary to diabetic SJS, which may also involve the atlanto-occipital joint.

diabetic recipients substantiates this impression. Age at onset of diabetes was recorded inconsistently in our patients; thus, duration of disease could not be evaluated as a factor. The degree of correlation between SJS of the hand, atlanto-occipital joint mobility, duration of diabetes, and ease of laryngoscopy is now under prospective investigation.

The incidence of difficult laryngoscopy in nondiabetic kidney recipients was fivefold greater than the institutional norm. Factors other than diabetes may increase the renal patient's chances of airway complications. Renal osteodystrophy or connective tissue disorders, for example, may be associated with CRF. This could not be analyzed in the present investigation.

Patients with CRF frequently have co-existing conditions that complicate airway management, including friable tissues, bleeding diatheses secondary to azotemia, and mucosal edema caused by hypoproteinema, and fluid retention. Other intercurrent medical problems (electrolyte imbalance, hypertension, congestive heart failure, drug effects) make the CRF patient especially intolerant of airway loss. Autonomic instability, gastric atony and hyperacidity, and

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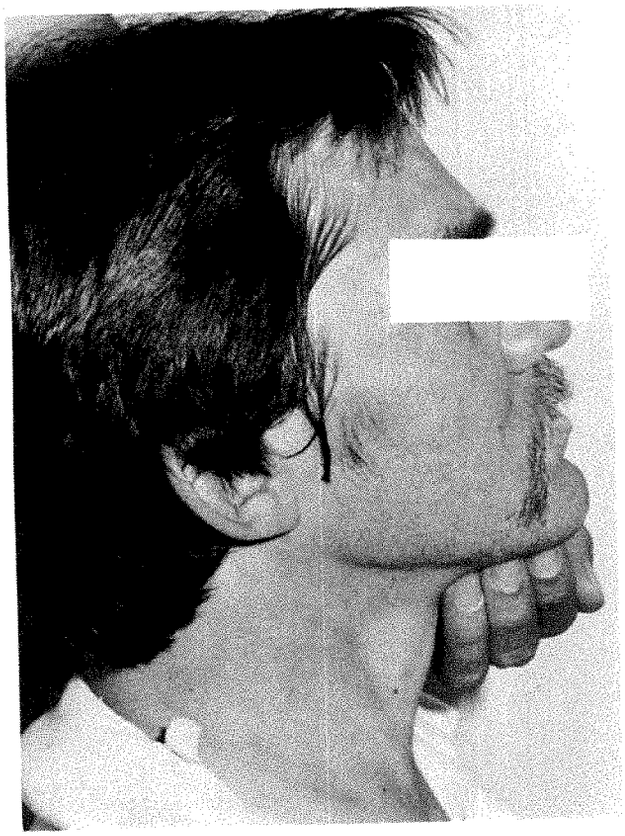

Figure 2. Profile of the patient in Figure 1 showing apparently normal external airway anatomy. Only the tip of the epiglottis was seen on direct laryngoscopy, and he was intubated blindly on the third attempt.

advanced coronary and cerebrovascular disease place the diabetic CRF patient at maximum jeopardy. Preoperative preparation of cadaveric recipients is often hasty and incomplete since the time of extracorporeal renal perfusion is limited. Postponement or cancellation of surgery may not be possible without sacrifice of the transplant opportunity, and tissue crossmatches may not be duplicable. Accordingly, preoperative assessment and planning for airway management becomes paramount.

Much remains uncertain regarding the connection of diabetes with difficult laryngoscopy. Because patients were not prospectively screened for SJS, the degree of correlation between SJS and difficult laryngoscopy cannot be stated with precision. Nor is it known whether the conditions responsible for difficult laryngoscopy in diabetic patients are arrested or reversed with pancreas or kidney transplantation. The exact incidence of this association and its attendant features await corraboration from other transplant centers.

Pancreas and kidney transplants are performed with increasing frequency and success. Survivors will require elective and nonelective anesthesia for related (e.g., transplant pancreatectomy) and unrelated procedures. If physical findings suggest SJS, flexion-extension radiography of the cervical spine is warranted. Limited atlanto-occipital extension should be considered an indication for measures to avoid pulmonary aspiration of gastric contents, including awake tracheal intubation with or without fiberoptic bronchoscopy.

The statistical assistance of Elizabeth Schiferl and secretarial assistance of Denise Roberts are gratefully acknowledged.

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Hemodynamic Effects of Nifedipine in a Canine Model of Acid Aspiration

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GRIFFETH JK, GALLAGHER TJ, PACKER DL. Hemodynamic effects of nifedipine in a canine model of acid aspiration. Anesth Analg 1988;67:1166–8.

A solution of ethyl alcohol, polyethylglycol, and distilled water that did (n = 5) or did not (n = 5) contain 250 μg/kg of the calcium channel blocker, nifedipine, was infused into the right atrium in 10 healthy mongrel dogs. Hydrochloric acid (pH = 1.8), 2 ml/kg, was then instilled into both lungs of all dogs via the tracheal tube. Hemodynamic data were collected before and 10 minutes after nifedipine was infused and 10, 45, 90, and 180 minutes after acid was instilled into the lungs. Gas exchange, including PaO_2 and venous admixture, did not differ between the two groups. However, after aspiration, oxygen delivery significantly improved in the dogs given nifedipine compared to oxygen delivery in those not treated with nifedipine. We conclude that, despite significant decreases in PaO_2 and venous admixture, nifedipine can restore oxygen delivery back to normal levels.

Key Words: LUNG, ASPIRATION.
PHARMACOLOGY, CALCIUM CHANNEL BLOCKERS—nifedipine.

Pulmonary aspiration of gastric contents causes pulmonary hypertension and hypoxemia (1), but it is unclear whether pulmonary hypertension results from hypoxemia or contributes to it. In one study of isolated canine lungs, increases in mean pulmonary artery pressure (PAP), ratio of wet-to-dry lung weight, and venous admixture were attenuated when the affected lobe was perfused with vasodilators such as sodium nitroprusside (2). The purpose of the present study was to evaluate the effect of the calcium channel blocker, nifedipine, which has peripheral and central vasodilating characteristics (3), on hemodynamics and gas exchange in a canine model of acid aspiration.

Materials and Methods

Ten healthy mongrel dogs (17–28 kg) were anesthetized with pentobarbital, 15 mg/kg, which was followed by a continuous infusion to maintain anesthesia. Tracheal intubation was accomplished with an 8-mm internal diameter tube with the distal tip placed above the carina with the animals in the supine position. Mechanical positive pressure ventilation was applied (tidal volume, 12–15 ml/kg) at a rate of 10 breaths/min (F_IO_2 = 0.24). Ringer's lactate solution was administered at 2 $ml^{-1} \cdot kg^{-1} \cdot min^{-1}$. A 7 Fr balloon-tipped, flow-directed, thermodilution pulmonary artery catheter (American Edwards Laboratory) was inserted via the left internal jugular vein and a thermistor-tipped catheter (American Edwards Laboratory) was placed in the left carotid artery for calculation of extravascular lung water (EVLW), also by thermodilution. Mean arterial pressure (MAP), pulmonary capillary wedge pressure (PCWP), PAP, EVLW, cardiac output (CO), and arterial oxygen tension (PaO_2) were measured. Arteriovenous oxygen content difference ($C[a\text{-}v]O_2$), venous admixture ($\dot{Q}sp/\dot{Q}t$), oxygen delivery (DO_2), cardiac index (CI), and systemic and pulmonary vascular resistances (SVR, PVR) were calculated by standard formulae.

After baseline measurements, the right atrium of each dog was infused with a solution of 15% ethyl alcohol, 15% polyethylene glycol 400, and 60% distilled water (by weight) with (n = 5) or without (n = 5) 250 μg/kg of nifedipine over 2 to 3 min. Measurements were repeated 10 minutes after the infusion was discontinued. Then, hydrochloric acid (pH 1.8),

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Table 1. Pulmonary Effects of Aspiration With and Without Pretreatment with Nifedipine

	Control		10 min after infusion		Time after aspiration (min) 10	
	Without nifedipine	With nifedipine	Without nifedipine	With nifedipine	Without nifedipine	With nifedipine
Arterial oxygen tension (mmHg)	109 ± 31	106 ± 10	83 ± 6	104 ± 11	46 ± 8[a]	47 ± 7[a]
Arteriovenous oxygen content difference (ml/100 ml)	2.9 ± 0.3	2.4 ± 0.4	2.5 ± 0.1	2.5 ± 0.4	3.2 ± 0.8	1.9 ± 0.3[b]
Oxygen delivery (ml O_2/min)	55 ± 18	65 ± 30	51 ± 40	94 ± 40[a]	35 ± 19[a]	59 ± 17[b]
Venous admixture ($\dot{Q}sp/\dot{Q}t$) (%)	7 ± 12	5 ± 5	16 ± 6	8 ± 6	56 ± 13[c]	68 ± 5[a]
Extravascular lung water (ml/kg)	11 ± 2	10 ± 3	11 ± 1	8 ± 2	19 ± 8	10 ± 2
Cardiac index	4.9 ± 0.7	5.1 ± 1	5.1 ± 0.2	7.3 ± 2*	4.5 ± 1	6.2 ± 1[a,b]
Pressures (mmHg)						
Mean arterial	111 ± 20	118 ± 12	100 ± 10	52 ± 17[a,b]	84 ± 16[a]	67 ± 7[a]
Pulmonary artery	12 ± 3	16 ± 8	17 ± 1	19 ± 9	16 ± 3	16 ± 5
Pulmonary capillary wedge	2 ± 1	6 ± 4	5 ± 0.7	8 ± 3	3 ± 1	6 ± 3
Vascular resistances (dyne/sec/cm^{-5})						
Systemic	2320 ± 199	2098 ± 463	1972 ± 198[a]	592 ± 163[a,b]	2065 ± 843	973 ± 375[a,b]
Pulmonary	237 ± 54	184 ± 48	249 ± 46	130 ± 59	288 ± 75	147 ± 36[b]

2 ml/kg, was instilled into the tracheal tube of all animals while they were in the left and then the right lateral decubitus positions. The total amount injected was 4 ml/kg. Data were then collected 10, 45, 90, and 180 minutes after tracheal instillation of the acid.

Data were subjected to paired Student's *t* test and regression analysis. This study was approved by the animal experimentation committee at the University of Florida.

Results

In both groups $\dot{Q}sp/\dot{Q}t$ increased (Table 1) with acid aspiration, whereas EVLW remained unchanged except at 180 minutes. Throughout the remainder of the study, after aspiration PVR and SVR were significantly lower in the nifedipine-group than in the untreated group ($P < 0.05$). CO in the nifedipine group was maintained at significantly higher levels than in the untreated group. $\dot{Q}sp/\dot{Q}t$ and PaO_2 did not differ between groups, which resulted in a significantly greater arteriovenous oxygen content difference (DO_2) in the nifedipine group.

Discussion

Nifedipine did not appear to modify the cardiopulmonary responses to the tracheal instillation of acid inasmuch as $\dot{Q}sp/\dot{Q}t$ increased to the same extent in both groups. Previous data indicated that an increase in cardiac index can worsen $\dot{Q}sp/\dot{Q}t$ secondary to increased blood flow (4,5), but this did not appear to be the case in our study. Because $\dot{Q}sp/\dot{Q}t$ was greater than 40%, even the increase in blood flow may have not been enough to cause any further deterioration.

That values for PAP and PCWP did not differ between the two groups probably indicates that nifedipine did not influence capillary permeability (6). Identical pressures and alterations of permeability would be expected to result in identical amounts of EVLW (7). Some data suggest that increased CI might recruit more exchange areas in the lung and, therefore, ultimately increase EVLW (8). This may explain the inconsistent but significant changes in EVLW seen at 10 and 180 minutes after aspiration.

The increased CI in the nifedipine group contributed to the overall increase in DO_2. The peripheral dilating effects of nifedipine likely helped to reduce MAP and SVR, which then secondarily enhanced CO (9). On the other hand, PAP was not affected by nifedipine.

Two factors may have contributed to the increased CI in the nifedipine-treated group. While not a statistically significant effect, the mean PCWP was always higher in the nifedipine group. More likely, CI increased because MAP and SVR decreased in this group. This can decrease afterload and improve myocardial performance (9). There is no evidence that nifedipine directly enhances cardiac function. Fur-

Table 1. *continued*

45		90		180	
Without nifedipine	With nifedipine	Without nifedipine	With nifedipine	Without nifedipine	With nifedipine
54 ± 4[a]	65 ± 8[a,b]	54 ± 6[a]	67 ± 6[a,b]	58 ± 11[a]	68 ± 4[a]
3.2 ± 0.8	1.8 ± 0.6[b]	2.7 ± 0.5	1.8 ± 0.3[b]	4.1 ± 1.7	1.8 ± 0.4[b]
360 ± 13[a]	910 ± 22[a,b]	370 ± 13[a]	820 ± 25[a,b]	390 ± 13[a]	780 ± 22[a,b]
47 ± 9[a]	49 ± 11[a]	51 ± 11[a]	49 ± 9[a]	37 ± 15[a]	43 ± 17[a]
18 ± 6	10 ± 4	19 ± 8	11 ± 2	23 ± 9[b]	13 ± 2[a,b]
4.2 ± 1	7.3 ± 1[b]	4.2 ± 1	6.3 ± 1[b]	4.0 ± 1	6.2 ± 1[a,b]
81 ± 20	79 ± 18[a]	93 ± 14	79 ± 11[a]	117 ± 20	92 ± 7[a,b]
14 ± 4	20 ± 7[a]	18 ± 9	19 ± 8[a]	15 ± 6	19 ± 7
2 ± 1	8 ± 5	4 ± 4	7 ± 3	2 ± 2	6 ± 3
1988 ± 695	915 ± 222[a,b]	2703 ± 1071	1104 ± 26[a,b]	3575 ± 706[a]	1331 ± 386[a,b]
298 ± 81	149 ± 20[b]	419 ± 277	171 ± 35	404 ± 187	184 ± 32[b]

Values are mean ± SD.
[a] $P < 0.05$ compared with control.
[b] $P < 0.05$ compared with solution without nifedipine.

thermore, the response of the pulmonary circulation to increased flow (CI) includes a modest increase in pressure; but because of recruitment of alveoli and distention of the pulmonary vessels, resistance actually decreases. The decrease in PVR also may be caused by nifedipine.

In this study, the major benefit of pretreatment with nifedipine appeared to be enhancement of CI and elevation of DO_2. Unlike a previous study with nifedipine (10), the dosage and administration schedule of nifedipine used had no adverse effect on pulmonary hemodynamics or gas exchange but, rather, enhanced overall cardiovascular performance and improved DO_2 in a canine model of acid aspiration.

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Analgesic and Hyperalgesic Effects of Midazolam: Dependence on Route of Administration

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NIV D, DAVIDOVICH S, GELLER E, URCA G. Analgesic and hyperalgesic effects of midazolam: dependence on route of administration. Anesth Analg 1988;67:1169–73.

The effects of intraperitoneal (IP) and lumbar intrathecal (IT) midazolam (MID) on nociception was studied in 38 male albino rats using the noxious tale-flick and hot-plate tests. Four groups received IP 0.1, 1, and 10 mg/kg MID or an equal volume of its vehicle benzyl alcohol 0.1 mg in 1 ml saline, while the other three groups received IT 10 and 100 μg MID or 0.5 μg benzyl alcohol in 5 μl saline. The two higher doses of IP MID produced statistically significant decrease of tale-flick latencies ($P < 0.005$ and 0.05 at 10 and 100 mg/kg MID, respectively). This hyperalgesic effect could be seen, although the animals appeared highly sedated with reduced motor activity and relatively unresponsive to non-noxious stimuli. In contrast, IT injections of 10 μg MID produced moderate but statistically significant prolongation of tail-flick latencies ($P < 0.05$) without noticeable change in motor activity. This analgesic effect could not be observed with the higher dose of IT MID until an hour after its administration. The almost complete immobility and ataxia seen after the high doses of IP and IT MID (animals lying on their sides) precluded reliable hot plate testing in these animals. Apparently part of the high IT dose of MID diffused into the brain, as observed after high-dose IP administration. We therefore propose that the analgesic effect of midazolam stems from its action at the spinal level, while its sedative and hyperalgesic effects are a function of its supraspinal action.

Key Words: HYPNOTICS, BENZODIAZEPINES—midazolam.

Benzodiazepines (BDZ) are widely used in medical practice; their potent sedative, myorelaxant, anticonvulsant, and (especially) anxiolytic properties are well-established (1). The effects of BDZ on responses to painful stimuli, however, are not well-defined. Administration of parenteral BDZ to laboratory animals has led to controversial results when analgesia was tested (2,3). Similar lack of clarity exists when BDZ analgesia is examined in humans. It is common clinical experience that the systemic administration of BDZ is often insufficient for overcoming pain and discomfort associated with diagnostic or minor surgical procedures (gastroscopies, colonoscopies, bronchoscopies, tooth extraction, etc.) and that the concomitant use of local anesthetics or opioid drugs is needed (4,5). On the other hand, several reports suggesting depression of nociception by systemic BDZ have been published. For example, diazepam sedation during surgical extraction of third molars performed under local anesthesia abolished the norepinephrine response to surgery (6), and diazepam or midazolam administration for induction of anesthesia is associated with reduction of cardiovascular responses to intubation (7,8). More convincing evidence for the ability of BDZ to produce analgesia has been provided by showing that the lumbar intrathecal administration of midazolam, the water-soluble BDZ, in anesthetized dogs depresses sympathetic reflexes evoked by nociceptive stimulation of the animals' hind- but not forelimbs (9). This effect was completely reversed by the BDZ antagonist RO 15-1788, strongly suggesting that such inhibition is mediated via spinal cord BDZ receptors. More impressive is the fact that, for humans undergoing abdominal or thoracic surgery, epidural administration of midazolam produces marked analgesia (10).

It thus appears that the different effects of BDZ on nociception may depend on the route of administration, with analgesia observed after spinal application, but not after systemic administration of these agents. The purpose of this study was to examine whether in

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rats such differential effects on responsiveness to noxious heat can be demonstrated.

Methods

Experiments were performed on 38 male albino, Charles River–derived rats weighing 350 to 450 g. Three groups of animals (six rats in each group) were prepared for intrathecal (IT) injections and the rest, divided into four groups (five rats in each group), received intraperitoneal (IP) injections.

Implantation and injection procedures

For direct spinal application of midazolam, animals were prepared surgically, with a chronic cannula implanted as described by Yaksh and Rudy (11). Rats were anesthetized with IP methohexital (30–40 mg/kg), after which polyethylene tubing (PE-10) was inserted 8.5 cm into the subarachnoid space through a slit in the cisternal atlanto occipital membrane so that the tip lay in the lumbar region. The cannula was fixed to the skull with dental acrylic and secured by stainless steel screws.

After at least 5 days of recovery, the effects of the BDZ agonist, midazolam, on nociception were examined. Midazolam (10 or 100 μg) or its vehicle (0.9% saline with 0.1% benzyl alcohol) was injected intrathecally in a volume of 5 μl, followed by 10 μl of saline to flush the drug solution from the cannula. Solutions were injected over a period of 1 min.

Intraperitoneal injections consisted of equal volumes (1 ml) of either midazolam 0.1, 1, and 10 mg/kg, or its vehicle (saline with 0.1% benzyl alcohol).

Assessment of nociceptive threshold

Responsiveness to noxious heat was assessed by measuring spinal reflex withdrawal (the tail-flick method) and supraspinal responses (the hot-plate method). Tale-flick latencies were determined by placing the animal's tail over a heat source (150 W halogen quartz lamp) and measuring the time elapsed between heat source activation and tail withdrawal. Heat source activation was ended automatically after 10 s if the animal had not removed its tail by that time. Hot-plate response was measured by placing the animal on a heated (57°C) metal surface, surrounded by a 20-cm diameter, 30-cm high plexiglass enclosure, and measuring the latency to licking of the hindpaw.

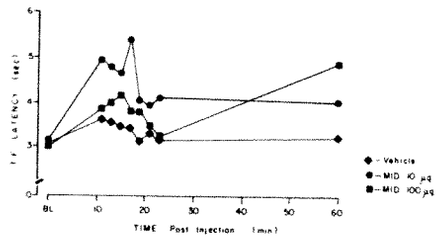

Figure 1. Mean tail-flick (T.F.) latencies at different intervals following the intrathecal injection of midazolam (MID) or its vehicle. Two of the tested groups were treated with midazolam 10 and 100 μg respectively, and the third group had equivolume saline with benzyl alcohol.

Testing protocol was as follows: The animals were placed in a Plexiglas restrainer for 5 min of adaptation, followed by five tail-flick determinations at 2-minute intervals, after which the animals were placed on the hot plate and responses noted. Animals then received midazolam (either intraperitoneally or intrathecally) and their motor behavior was monitored for 10 minutes. The animals were then replaced in the restrainer and seven tail-flick determinations were made at 2-minute intervals, immediately after which the hot-plate test was administered again. Additional tail-flick determinations were then made 60 minutes after drug administration.

All data were analyzed using analysis of variance for repeated measures with baseline tail-flick latencies as a covariate. The time course of drug action in those groups showing a significant main effect was evaluated by comparing tail-flick values at every time period with the corresponding values in vehicle pretreated animals.

Results

Analysis of variance of the tail-flick data reveals a significant drug effect ($P < 0.05$), demonstrating the analgesic effect of intrathecally administered midazolam (Fig. 1). Comparison with vehicle-injected controls reveals that significant analgesia can be produced by both 10 μg ($P < 0.02$) and 100 μg ($P < 0.05$) of the drug. However, a different time course of midazolam-induced analgesia is evident with the two doses employed. During the first 30 min after intrathecal drug administration, a significant ($P < 0.01$) analgesic effect was observed with the lower dose of midazolam (10 μg) but not with the higher dose. Peak analgesia occurred within 10 minutes, with paired comparisons revealing significant increases in tail-flick levels ($P < 0.05$) averaging 50% above control levels. Significant analagesia persisted for 10 minutes, after which values returned to baseline levels

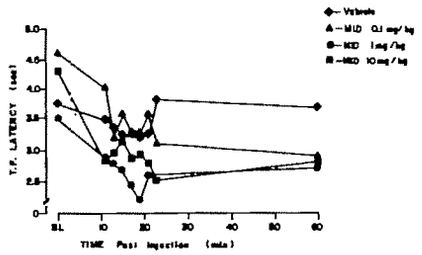

Figure 2. Mean tail-flick (T.F.) latencies at different intervals following the intraperitoneal injection of midazolam (MID) or its vehicle. Three of the tested groups were treated with midazolam at doses of 0.1, 1, and 10 mg/kg, respectively, and the fourth group had equivolume saline with benzyl alcohol.

for the remainder of the testing period. In contrast, after 100 μg of midazolam, significant analgesia ($P < 0.05$) was observed 60 minutes after intrathecal drug administration but not any earlier. Thus, a 54% increase in tail-flick latencies was present, an effect comparable to the peak analgesic effect of the lower dose observed earlier after injection.

Differences in motor behavior were seen in animals receiving the two doses of intrathecal midazolam. While animals given the lower dose appeared active and did not differ in their activity from the animals receiving IT vehicle solution, animals given 100 μg of midazolam were sedated and ataxic within 2 min of IT injection. Ten minutes after injection these animals appeared sedated, somnolent, and immobile, often lying on their sides, paws failing to contact the surface of the hot plate when placed upon it. These motor effects precluded reliable hot plate testing in these animals. In contrast, tail-flick latencies in the same animals were within baseline values.

Hyperalgesia, not analgesia, resulted when midazolam was administered intraperitoneally (Fig. 2). This effect was due to a significant decrease of tail flick latencies induced by both 1 mg/kg ($P < 0.005$) and 10 mg/kg ($P < 0.05$) of midazolam. A decrease of tail-flick values seen after 1 mg/kg of the drug appeared within 5 minutes of drug injection ($P < 0.01$) peaked 20 min after intraperitoneal injection and was not significantly different from baseline values 60 minutes after injection. A dose-related decrease in motor activity was also seen with IP midazolam. Almost complete immobility and ataxia with most animals lying on their sides were seen after 10 mg/kg of the drug, again (as was the case of animals receiving high concentrations of intrathecal midazolam) not permitting a valid evaluation of hot-plate latencies.

Discussion

Intrathecal injection of midazolam produced analgesia, as measured by the tail-flick test, an effect more prominent with the low dose of the drug. In contrast, intraperitoneal injection of midazolam produced hyperalgesia, which was manifested as a decrease in tail withdrawal latency.

The fact that the analgesia observed after IT midazolam administration was not correlated with impairment of somatic motor function produced by the drug mitigates against the possibility that decreased motor activity may account for the analgesic effect observed. Indeed, no analgesia was observed during a time in which profound motor depression was present, as was the case after IT injection of 100 μg of midazolam. Significant analgesia could be detected only after 60 minutes from the IT injection. At that time, most of the sedative and immobilizing effects of the drug had worn off.

The hypnotic and sedative affects of benzodiazepines are attributed to effects of these drugs within the brain (1–3). The induction of both somnolence and sedation by a high concentration of intrathecal midazolam suggest that at these high concentrations diffusion of significant quantities of the drug into the brain occurs. In contrast, the lack of a sedative effect after 10 μg of intrathecal midazolam may indicate reduced supra spiral action of the drug.

These data, taken together with the hyperalgesic effect of intraperitoneal midazolam, suggest that the analgesic effect of the midazolam stems from its action at the spinal level, while its sedative and hyperalgesic effects are a function of its supraspinal action. Such a hyperalgesic supraspinal effect predominates when midazolam reaches both spinal and supraspinal sites, as was the case after injection of the high dose of intrathecal midazolam or after its intraperitoneal administration. Similar antagonistic spinal-supraspinal interactions have recently been reported for barbiturates (12). Interestingly, barbiturates are known to act at the same GABA-barbiturate-BDZ receptor complex at which BDZs are known to act (13,14).

The analgesia observed after intrathecal injection of midazolam, similar to that reported in a study in awake rats (15), agrees with electrophysiological studies in animals showing reduction of both mono- and polysynaptic reflex activity after intrathecal midazolam or diazepam (9,16–20). The latter depression is not limited to reflex activity but can also be seen in axons ascending in the ventrolateral spinal cord known to conduct nociceptive impulses (20). Thus, not only are spinal reflexes attenuated but conduction of noxious impulses to supraspinal structures is also reduced, a finding well in line with the reported analgesic effect of intrathecal midazolam in humans (10).

Our results suggest that BDZ can produce both supraspinal hyperalgesic and spinal analgesic effects. Simultaneous activation of both sites will result, at higher doses, in a predominantly hyperalgesic effect, which indicates that supraspinal structures can override the effect obtained at the spinal level. In view of these facts, it is possible that the lack of analgesic action of BDZ, seen both clinically and experimentally, may stem from the systemic route of administration of the drug.

It has been shown that BDZ may reduce the affinity of γ-amino-butyric acid (GABA) for its presynaptic receptors and thus facilitate its synaptic action (21). In addition, recent studies have shown that GABA not only enhances morphine analgesia (22), but itself has analgesic properties (23,24) and is found in high concentrations in the dorsal root area (25). Midazolam therefore, when applied intrathecally, might have gained access to analgesic systems mediated by GABA. The supraspinal mode of action may be different. It is known that the brain levels of endogenous opioids increase significantly in response to stress (26,27). Moreover, stress is often associated with anxiety and fear, raising the possibility that endogenous opioids released under these conditions may interfere in adaptation to stress. BDZ with their anxiolytic properties might therefore play a role in attenuating those effects of endogenous opioids, thus diminishing nociceptive inhibitory mechanisms. This hypothesis is supported by a recent study showing evidence that a BDZ receptor mechanism regulates the secretion of pituitary β-endorpine (28). A corollary investigation resulting from the present data will be to test responses to nociception following BDZ applications at various supraspinal sites.

Although the clinical significance of systemic BDZ hyperalgesia remains obscure, the intrathecal findings with BDZ suggests a possible additional group of drugs capable of inducing regional analgesia.

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Sixty-Five Years Ago In

Anesthesia & Analgesia

L. A. Oldenbourg: A Preliminary Report on Ethyl Chlorid (sic) Anesthesia in Minor Operations. Current Researches in Anesthesia and Analgesia: 1923;2:30.

Three aspects of this article are of interest to the modern anesthesiologist. First, it is another example of the continued and often imaginative quest for the perfect anesthetic that started after the introduction of ether in 1846. Second, the paper described what must surely be the most rapidly acting anesthetic ever used clinically. Ethyl chloride is non-irritating to the airway and has a boiling point of 12.5° C (a liquid in a glass cartridge, it vaporizes immediately when sprayed at room temperature onto a surface) and low solubility in water or blood. The author, using a closed system, anesthetized her patients (adults and children) to the point of complete relaxation, dilated pupils and absent corneal reflec with only 3-4 breaths. The face mask was then taken off and the operation (T and A) was performed. And, third, the time from the start of anesthesia to the completion of surgery and return of consciousness averaged 4-5 minutes. Rapid onset, rapid recovery, yes, but a T and A in 2-3 minutes? (Memories of personal introduction to the use of this technique in 1949 include being told to spray the ethyl chloride onto the cloth open-drop mask till the next to last breath—about 3-4 breaths.). Just the anesthetic for out-patient surgery today? Some will remember use of ethyl chloride to produce local cryo-anesthesia by spraying on the skin. The liquid vaporizes so fast the skin is frozen. Effective but ephemeral local anesthesia; not, however, to be used for topical anesthesia on the face—as interns in the E.R. annually had to learn in bygone years.

Minimum Alveolar Concentration of I-653 and Isoflurane in Pigs: Definition of a Supramaximal Stimulus

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EGER EI, JOHNSON BH, WEISKOPF RB, HOLMES MA, YASUDA N, TARG A, RAMPIL IJ. Minimum alveolar concentration of I-653 and isoflurane in pigs: definition of a supramaximal stimulus. Anesth Analg 1988;67:1174–6.

We determined the anesthetic potencies of a new fluorinated anesthetic, I-653, and isoflurane in pigs as a preliminary to a study of the relative cardiovascular and electroencephalographic effects of these agents. Clamps were sequentially applied to the dew claw and/or tail of each animal to determine the minimum alveolar concentration (MAC) that suppressed movement in response to each of these stimuli. MAC obtained by clamping the tail (8.28 ± 1.34% [mean ± standard deviation] for I-653 and 1.65 ± 0.36% for isoflurane) was more variable and lower than MAC obtained by clamping the dew claw (10.00 ± 0.94% for I-653 and 2.04 ± 0.19% for isoflurane). We conclude that the type of stimulus applied affects the MAC value obtained for I-653 and isoflurane. Clamping the tail is not a supramaximal stimulus in pigs; a greater stimulus is provided by clamping the dew claw.

Key Words: ANESTHETICS, VOLATILE—I-653, isoflurane. POTENCY, ANESTHETIC—I-653, isoflurane.

The compound I-653 is a new fluorinated inhaled anesthetic whose low solubility (blood/gas partition coefficient of 0.42 in humans) (1) produces a more rapid recovery than that obtained with other potent inhaled anesthetics (2). I-653 is more stable in soda lime (3) and is less metabolized (4) than other anesthetics, including isoflurane. It is nontoxic when administered repeatedly (5), and no more toxic than isoflurane in hypoxic rats whose hepatic microsomal enzymes have been induced by administration of phenobarbital (6).

The favorable characteristics of I-653 led us to consider undertaking a study of the cardiovascular and electroencephalographic effects of I-653 in pigs, and a comparison of these effects with those produced by isoflurane. As a preliminary, we first had to determine the MAC of I-653 and isoflurane in the pigs to be studied. We now present the data from these MAC studies for the following reasons: MAC values of I-653 have not been previously reported for swine; our results for isoflurane differ from those presented by other investigators (7); and our data confirm (7) that different stimuli can result in different MAC values in pigs.

Materials and Methods

Our study of 13 juvenile domestic pigs weighing 14 to 22 kg and aged 3 to 4 months was approved by the UCSF Committee on Animal Research. Anesthesia was induced using I-653 in oxygen given via a mask. Once induction was complete (as defined by absence of movement and lash reflex), succinylcholine, 2 mg/kg, was given i.v. and a cuffed endotracheal tube placed. Ventilation was controlled to maintain end-tidal carbon dioxide levels between 5 and 5.2%. Pulmonary artery blood temperature was maintained between 38.0°C and 39.5°C. (Average 38.7 ± 0.3°C). On a separate day, nine of these pigs were anesthetized using isoflurane in oxygen given via a mask, and the same protocol maintained.

A MAC of I-653 and isoflurane was determined as previously described (8), using infrared analysis for

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both agents. A Beckman® LB-2 analyzer was used to measure I-653. Despite modifications of the sampling head, we could not obtain linearity with this device. Thus, we constructed a calibration curve from primary standards. Isoflurane was analyzed using a Puritan-Bennett® Anesthetic Agent Monitor 222 that provided a linear response over the range of isoflurane concentrations used. For each study both devices were calibrated with secondary (tank) standards.

Gas samples for carbon dioxide and anesthetic analyses were obtained from the proximal portion of the endotracheal tube. Values obtained for MAC were corrected for condensation of water vapor, assuming that the sample temperature approximated room temperature. Correction also was made for barometric pressure, which ranged from 757 to 768 mmHg.

Using the "standard" tail clamp technique (8), we found MAC values of approximately 8% in the first two pigs, but obtained a lower value (7%) in the third. Serendipitously, we applied the clamp to the dew claw of the third pig at the concentration that had suppressed movement in response to clamping the tail. Vigorous movement followed, and MAC in this pig (10.6%) was subsequently measured using stimulation of the dew claw. Our experience with the fourth pig was similar: tail clamp MAC, 7.7%; dew claw clamp MAC, 9.6%. We determined the MAC of I-653 and isoflurane in the ensuing nine pigs by applying a clamp to the dew claw and, separately, by applying a clamp to the tail.

For both stimuli, MAC was determined in the standard manner, usually in duplicate (8). The response to clamping the tail was tested first at each anesthetic concentration with at least 1 minute of recovery before clamping the dew claw. Movement solely of the extremity clamped was not sufficient to grade a response positive; movement of another part of the animal was required. MAC was calculated as the mean of the concentrations just preventing or permitting movement, ie, the bracketing values. However, in four pigs, a positive response was not obtained with application of a clamp to the tail at concentrations of I-653 and/or isoflurane that permitted spontaneous movement and/or vigorous movement in response to application of a clamp to the dew claw. We did not test lower concentrations in these pigs, but assumed the MAC value obtained by clamping the tail to be equal to the value to be obtained if movement occurred with the next decrement in alveolar concentration (approximately 20% of the previous alveolar concentration). Consequently, we may have overestimated the MAC value obtained by clamping the tail and underestimated the variance of this value.

Table 1. MAC (% of 1 Atm) Values Obtained with Different Stimuli in Pigs[a]

Stimulus	I-653	Isoflurane
Tail clamp	8.28 ± 1.34	1.65 ± 0.36
(N)	(13)	(9)
Dew claw clamp	10.00 ± 0.94	2.04 ± 0.19
(N)	(11)	(9)
Temperatures (°C)	38.6 ± 0.2	38.8 ± 0.4

[a]Values are presented as the means ± standard deviation.

The means and standard deviations for tail clamp MAC and dew claw clamp MAC for each anesthetic were calculated. The results for tail clamp MAC and dew claw clamp MAC were compared using a paired Student's *t*-test. Differences were considered statistically significant at $P < 0.05$.

Results

The MAC value obtained for I-653 or isoflurane with the dew claw clamp was greater than that obtained with the tail clamp in nine of 11 pigs, and identical in two pigs. However, the response to stimulation of the dew claw in the latter two pigs always was more vigorous than the response to stimulation of the tail. One pig failed to respond to the tail clamp at 1.03% isoflurane. With I-653, the average MAC value obtained by clamping the dew claw was 21% greater than that obtained by clamping the tail; with isoflurane, the difference was 19% (Table 1). For both anesthetics, this difference was significant ($P < 0.01$).

Discussion

Our value for isoflurane MAC obtained by clamping the tail (1.65 ± 0.36%) does not differ significantly from that of 1.45 ± 0.17% reported by Lundeen et al. (7) or that of 1.55 ± 0.28% reported by Eisele et al. (9). However, our value for MAC obtained by clamping the dew claw significantly exceeds both our value for tail clamp ($P < 0.01$; paired Student's *t*-test) and that given by Lundeen et al. or Eisele et al. (P 0.01; unpaired Student's *t*-test), despite the slightly higher body temperature maintained by Lundeen et al. (39.5°C) and possibly by Eisele et al. (38.5–39.5°C). The difference in isoflurane MAC determined by the two stimuli also characterized I-653 ($P < 0.01$). Thus, clamping the tail does not appear to provide a supramaximal stimulus in the pig. MAC obtained by tail

clamping also was more variable than MAC obtained by dew claw clamping. These data indicate that the use of the tail clamp stimulus probably results in an underestimate of the true anesthetic requirement in pigs. Consequently, previous studies of the MAC of other agents in pigs may underestimate MAC for those agents (10–12). In one such study, the investigators applied a clamp to the toe as well as the tail, but did not comment on any differences in response (12).

Lundeen et al. (7) found that the concentration of isoflurane required to suppress the "pedal reflex" ("application of a hemostat at the skinfold between the digits of the hind limb") was higher than the concentration required to suppress the response to a clamp applied to the tail (7). Our results support their conclusion that "neither (clamping the tail nor surgical incision) is a supramaximal stimulus. . . ." However, we cannot make precise quantitative comparisons between our results and theirs because they did not fully define MAC using the "pedal reflex." Their data suggest (see their Table 2) that the MAC of isoflurane obtained using the pedal reflex (approximately 2.2% isoflurane) is at least 50% greater than their value obtained using the tail clamp (1.45% isoflurane). This difference is greater than the difference we found, in part because we may have overestimated MAC using the tail clamp stimulus. (As noted above, we failed to define the lower bracketing concentration in four pigs.)

The difference in isoflurane MAC in pigs due to clamping the tail versus the dew claw is the reverse of that for clamping the tail versus the paw in dogs (8). If anything, clamping the paw yields a lower MAC value. One might speculate that the near-vestigial nature of the tail in the pig is associated with a lesser innervation and sensitivity than that found in the tails of dogs.

The MAC values for I-653 and for isoflurane obtained by stimulating the dew claw are higher than the MAC values obtained in other species. For example, clamping the tail in rats results in a MAC of 5.72% for I-653 (13). The higher MAC in pigs may be due to the age of the pigs (about 3 to 4 months old) (14,15) and the slightly higher (albeit normal) body temperature maintained in the present studies (13,16).

Our results may be used to predict the MAC of I-653 in humans. Our MAC for isoflurane in pigs is 1.8 times greater than the value of 1.15% reported for humans (15). If the same ratio applies to I-653, the MAC of I-653 in humans should be about 5.6%, approximately 1% greater than the human MAC value predicted from data obtained in rats (13).

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Clinical Reports

Relief of Sciatic Radicular Pain by Sciatic Nerve Block

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Key Words: PAIN, SCIATICA. ANESTHETIC TECHNIQUES, REGIONAL—sciatic block.

Many diseases and injuries produce low back pain that radiates into the peripheral sensory distribution of a nerve root. It is commonly believed that root damage resulting from compression and/or inflammation leads to the generation of impulses in the sensory fibers of the injured roots which are perceived as peripheral pain (1,2). In the radicular pain of sciatica, for example, ectopic impulses arising at the site of root injury are perceived as pain in the peripheral distribution of this nerve. We have seen, however, several cases of low back pain with sciatica in which block of the sciatic nerve distal to the site of the lesion with a local anesthetic produced complete and often long-lasting relief of pain in the distribution of the sciatic nerve. We present here cases demonstrating this phenomenon. These cases are not selected according to the response to the block of the sciatic nerve; they represent our outpatient population as a whole.

Method

The effect of sciatic nerve block on pain intensity in the sciatic nerve distribution was assessed with the use of the visual analog scale (3,4). The scale consists of a 100-mm horizontal line (at the left end of the line is "no pain at all" and, at the right, "as severe as it could be"). Pain intensity was determined before the block, and 20 minutes, 1 hour, and 2 hours after the block. If pain relief was present, the pain intensity was assessed three times (10:00 AM, 4:00 PM, and 10:00 PM) on the next day and once daily thereafter. The first four assessments were made in the pain clinic, and the other assessments were made by the patient at home using the visual analog scales. The form with the scales was returned to the physician during the next clinic visit. Sciatic nerve block was performed with lidocaine using the anterior approach to the nerve (5). Change in sensitivity to pinprick in the distribution of the sciatic nerve was used as an indicator of the blockade.

Case 1

The patient was a 24-year-old man with complaints of low back pain radiating to the right leg. The pain appeared 2 years previously, after a job-related injury caused by torquing a large bolt. During a 2-year period after the accident, the patient had constant pain. He was treated by two injections of epidural steroids with temporary pain relief after the first injection. He described his pain as a constant aching pain with intermittent burning and sharp pain components. The pain radiated to his right posterior thigh, calf, and foot. He also reported a tingling feeling in the right leg. Sensation to pinprick was decreased in the lateral calf and foot on the right. Straight leg raising test was positive at 60° on the right. Trigger points were found in the area over the right sacroiliac joint. The right Achilles tendon reflex was absent. Myelogram and computerized tomography (CT) scan were normal. The EMG study indicated L_5 radiculopathy. The patient's symptoms suggested a right L_5-S_1 radiculopathy.

This patient first received trigger point injections into the muscles of the right buttock, then, one month later, the right sciatic nerve was blocked with a local anesthetic. On both occasions the same amount of local anesthetic was used, 15 ml of 1%

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lidocaine. Immediately before the trigger point injection, the patient had a very low pain severity, a score of 10 mm on the 100-mm linear analog scale. Twenty minutes after the injection the pain disappeared completely. One hour after the injection the pain intensity level reached a score of 20 mm; in 2 hours, 50 mm, and in 5 hours, 70 mm. For the next 5 days the pain intensity level varied from 55 to 85 mm. The pain intensity level before the sciatic nerve block was 95 mm. Twenty minutes after the injection of lidocaine, sensitivity to pinprick throughout the sciatic nerve distribution had gone and the leg pain disappeared completely. The right lower limb was pain-free for 7 days. The block did not abolish the low back pain.

Case 2

The patient was a 57-year-old woman with complaints of low back pain radiating to the left leg. The patient had a lumbar laminectomy (L_5-S_1) 28 years ago. For the past 10 years the pain had increased gradually. The pain was located at the L_5 level over the middle of the spine, left paraspinal muscles, and the left buttock. The pain was described as sharp, shooting, and radiating to the left posterolateral thigh, calf, and big toe. Trigger points were found over the left sacroiliac joint and posterolateral border of the greater trochanter. The Achilles tendon reflexes were decreased symmetrically. The EMG study indicated L_5 radiculopathy. The diagnosis was L_5 radiculopathy after lumbar laminectomy.

The left sciatic nerve was injected with 15 ml of 1% lidocaine. Before the injection, pain severity was 85 mm on the 100-mm scale. Twenty minutes later, sensitivity to the pinprick in the distribution of the sciatic nerve disappeared and there was also complete pain relief. Two weeks later the patient was still free from the pain in the leg. At the same time the back pain was still present.

Case 3

The patient was a 37-year-old man with complaints of low back pain radiating into the left leg. He had a history of low back pain for 19 years. Eighteen years earlier he had undergone L_5-S_1 laminectomy, which provided some temporary pain relief. The pain was constant, mostly aching, radiating along the back of the left leg to the foot. Sensitivity to pinprick was decreased in the left L_5 distribution. The patella and Achilles tendon reflexes were bilaterally symmetrical. The straight leg raising test was positive at 30° on the left. An EMG study indicated left L_3 and L_5 radiculopathy. Myelography demonstrated an extradural defect at the L_5-S_1 interspace, probably secondary to osteophyte formation. The diagnosis was L_3 and L_5 radiculopathy after lumbar laminectomy.

The patient was given a left sciatic nerve block with 15 ml of 1 percent lidocaine. Before the injection, pain severity was 50 mm (100-mm scale). Twenty minutes after the block, when sensitivity to pinprick in the distribution of the sciatic nerve decreased, the pain completely disappeared. The patient remained pain-free for 1 week.

Case 4

The patient was a 40-year-old man with complaints of continuous burning and throbbing pain in the right leg from the buttock to the foot. The pain appeared 3 months earlier after the patient fell down a flight of stairs. Sensation to pinprick was decreased over the right thigh and calf. The patella and Achilles tendon reflexes were decreased on the right. The right thigh had a moderate degree of muscle atrophy. The straight leg raising test was positive on the right at 50°. There was tenderness over the right ileolumbar area and sciatic notch. An EMG study demonstrated changes indicative of L_5-S_1 radiculopathy. The diagnosis was L_5-S_1 radiculopathy.

Trigger point injection of 15 ml of 1% lidocaine was made into the muscles of the right buttock. Immediately before the injection, the patient's pain severity was 65 mm on a 100-mm scale. Twenty minutes after the injection the pain severity decreased to 25 mm and stayed at this level at 1 hour after the injection. Two hours after the injection, the pain returned to the preinjection level and remained at that level. One week later, the patient had a right sciatic nerve block with 15 ml of 1% lidocaine. Pain severity was 70 mm before the block. One hour after the block complete pain relief was achieved, except for the right big toe where some pain was felt. That degree of pain relief lasted approximately 2 hours, after which time the intensity of pain gradually increased but one week after the block, the pain was still less intense than before the block.

Case 5

The patient was a 41-year-old man with complaints of low back pain radiating to the left leg, including the

lateral calf and foot. Thirteen years earlier he had undergone lumbar laminectomy with temporary relief of pain. Several years later the pain gradually increased. The pain was constant and mostly aching. The patient also had weakness in the left leg and numbness over the lateral surface of the leg. Sensory testing showed decrease in sensitivity to pinprick over L_5 dermatome. Deep tendon reflexes were symmetrical. The straight leg raising test was positive at 70° on the left. Several trigger points were found over the muscles of the left buttock. An EMG study revealed left L_5 radiculopathy. Myelography and CT scan demonstrated evidence of the extradural defect at the L_5-S_1 level. The patient was thought to have left L_5 radiculopathy.

Trigger point injections into the muscles of the left buttock (15 ml of 1% lidocaine) did not change the level of the pain (70 mm on a 100-mm scale). Eight weeks later the patient had a left sciatic nerve block (15 ml of 1% lidocaine). Before the lidocaine injection, the pain intensity score was 90 mm; 20 minutes after the injection the pain decreased to a level of 15 mm and completely disappeared in 1 hour. The pain began to increase on the second day after the block and returned to the initial level of 90 mm on the third day after the injection. The sciatic nerve block did not give any significant relief of pain in the low back.

Discussion

We report five cases of low back pain radiating into the peripheral sensory distribution of the sciatic nerve. The radicular component of the pain was confirmed with needle EMG studies in all five patients. In all cases, sciatic nerve block produced complete pain relief in the sciatic nerve distribution despite the fact that the nerve block was at a point distal to the root injury. The described phenomenon contradicts the hypothesis that generation of impulses in sensory fibers of the injured root is the cause of the pain perceived in the peripheral distribution of the nerve. However, the possibility that lidocaine used for the sciatic nerve block reaches the injured root cannot be completely excluded.

One explanation for relief of pain due to nerve compression or irritation by a distal nerve block might be that the absorption of lidocaine from the site of the injection provides a sufficient plasma level of the agent that reaches the injured root and affects it. One study reported that intravenous administration of lidocaine up to 5 $mg \cdot kg^{-1}$ can provide complete pain relief in various chronic pain syndromes including low back pain with radicular symptoms (6). In our cases, such mechanism of action was unlikely. First, lidocaine was used for trigger point injections in the same dose as for sciatic nerve blocks (15 ml of 1% solution), but trigger point injections produced no pronounced pain relief. Although some decrease in the pain intensity was present in two out of three cases, it was very short-lived, no more than 20 and 60 min (cases 1 and 4, respectively), and probably should be regarded as a placebo effect. Second, after the sciatic nerve block, complete and long-lasting pain relief in the leg was not accompanied by a similar effect on low back pain, i.e., outside the distribution of the sciatic nerve.

Another possibility is that lidocaine may reach an injured root following sciatic nerve block through proximal spread of the drug along the sciatic nerve. In experiments with an injection of a radiolabeled local anesthetic into different compartments of the rabbit sciatic nerve, Selander and Sjöstrand (7) demonstrated that epineurial injection was associated with only limited proximal spread while endoneurial (intrafascicular) injection could lead to a rapid spread of anesthetic mainly between the nerve fibers. Although theoretically possible, it is not likely that peripheral sciatic nerve block may lead to proximal spread of lidocaine to a damaged root at L_5.

Our observations on pain relief following the sciatic nerve block may be explained by suggesting that sciatica associated with the root damage depends on the impulses arriving in the root from the periphery. Root damage only alters this probably normal afferent input in a way that gives perception of pain in the distribution of the sciatic nerve. In other words, sciatica that accompanies root damage depends on input from the periphery. It is possible to use several hypotheses to explain the mechanisms by which peripheral impulsation is altered in the injured roots. One of the hypotheses is based on the loss of segmental inhibition. Root injury may preferentially block the large myelinated afferents, which results in a disinhibition of the unmyelinated nociceptive input (8,9). Another hypothesis is that non-noxious impulses from the periphery arriving in the damaged root become switched into pain-signaling fibers, the so called cross-talk hypothesis (10,11). Finally, it is possible that normal afferent impulses from the periphery are amplified in the damaged root to the degree that they signal the pain (12). In any of these three mechanisms, cessation of the normal peripheral input to the damaged root will eliminate the pain.

The second phenomenon that we observed was a prolonged duration of pain relief that far outlasted the duration of sciatic nerve blocks in all five cases. The pain relief was especially pronounced in cases 1, 2, and 3; in cases 1 and 3 it lasted 1 week, and 2 weeks in case 2. This phenomenon is quite similar to many other observations that short duration local anesthetic blocks of nociceptive afferents, muscle trigger points, or sympathetic efferents may give prolonged pain relief (13). The suggestion of interruption of the "vicious circle" of self-sustaining pain put forth by Livingston (14) may explain this phenomenon.

A case of sciatica due to carcinomatous sacral root damage relieved by sciatic nerve block was reported by Kibler and Nathan (15). They also presented seven other cases where blockade of various peripheral nerves distal to the sites of their lesions produced pain relief. Our observations agree with the results reported by these authors.

The cases described in this paper indicate that when radicular pain in the sciatic nerve distribution represents a major symptom of backache, sciatic nerve block may be used to provide long-lasting relief for this symptom. However, it remains to be seen that the pain relief provided by the block distal to the site of lesion can actually decrease the root damage. It is impossible to exclude an opposite effect: that a pain-free state may lead to increase in the activities of a patient resulting in an additional root injury.

Relief of the radicular pain by sciatic nerve block suggests that sciatica associated with root damage cannot be explained only by ectopic impulses in the sensory fibers at the site of root injury. The pain perceived in the peripheral distribution of the sciatic nerve depends upon the impulses arriving at the site of the lesion from the periphery.

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Comparison of Interpleural and Epidural Anesthesia for Extracorporeal Shock Wave Lithotripsy

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Key Words: ANAESTHETIC TECHNIQUES—epidural and interpleural catheter technique. SURGERY, UROLOGICAL—extracorporeal shock wave lithotripsy.

Several types of anesthesia have been used for extracorporeal shock wave lithotripsy (ESWL). General or epidural anesthesia are more frequently used, but recently the combined use of intercostal blocks and local infiltration of the skin has been advocated. A new method for postoperative pain control after cholecystectomy, renal surgery, and breast operations has recently been described, involving the interpleural administration of local anesthetics through a catheter. The present study compares the interpleural technique with our standard epidural block technique with regards to pain relief, side effects, and circulatory stability during ESWL.

Material and Methods

The investigation was performed in accordance with the recommendation of the Helsinki Declaration and informed consent was obtained from each patient. It was approved by the local ethical committee. Patients with a history of pneumothorax, hemothorax, severe heart failure, or allergy to local anesthetics were excluded from the study.

Twenty patients who had to undergo ESWL took part in this open study. They were randomized into two groups given either an interpleural injection of 20 ml lidocaine 20 mg/ml or a lumbar epidural block with 22–25 ml mepivacaine 13 mg/ml. Meperidine (50–75 mg) IM was given 1 hr before anesthesia. A peripheral intravenous catheter was inserted, blood pressure, and the ECG were monitored. An epidural catheter was placed in 10 patients, and 22–25 ml mepivacaine 13 mg/ml (hospital-made solution) given with the patient in the lateral position (affected side down). In the other patients, who were in the lateral position (affected side up), an epidural catheter was placed in the pleural space using a 16-G Tuohy needle. The site of injection was 8–10 cm from the posterior midline. As the Tuohy needle advanced just over the rib, a well wetted, air-filled glass syringe was attached to the needle. After perforation of the parietal pleura, recognized by a "click," the plunger of the syringe moved forward because of the negative pressure in the pleural space during inspiration. The syringe was removed and an epidural catheter introduced 5–6 cm into the pleural space. After negative aspiration and attachment of a micropore filter 20 ml lidocaine 20 mg/ml was injected. Heart rate, mean arterial blood pressure (MABP), and respiratory rate were recorded both before and 5, 10, 15, 20, 30, 60, 120, and 240 minutes after the injection. Fentanyl and diazepam were given perioperatively in both groups as needed.

The extent of anesthesia by pinprick and the degree of pain assessed by a visual analogue scale (VAS 100 mm) were recorded at the same times MABP were measured. In addition, patients were asked postoperatively about discomfort during ESWL and whether they would like the same anesthesia if future ESWL was needed. A verbal rating of "severe," "moderate," and "no pain" was used.

Chest x-rays were taken on the first day postoperatively to check for possible pneumothorax. Statistical tests used included Fisher's exact test (for differences in use of analgetics and patient characteristics in the two groups), and Wilcox 2 sample test (for differences in the heart rate, respiratory frequency, and blood pressure). Pain assessment (VAS) was evaluated by repeated measure analysis. A level of $P < 0.05$ was considered statistically significant. The results are presented as mean ± SD.

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Table 1. Patient Characteristics

	n	Age (yr)	Height (cm)	Weight (hg)	Sex (f/m)	Shocks (No.)	Duration of ESWL (min)
Interpleural	10	53 ± 5	172 ± 2	70 ± 5	3/7	1692	44
Epidural	10	48 ± 5	167 ± 3	67 ± 4	7/3	1583	41

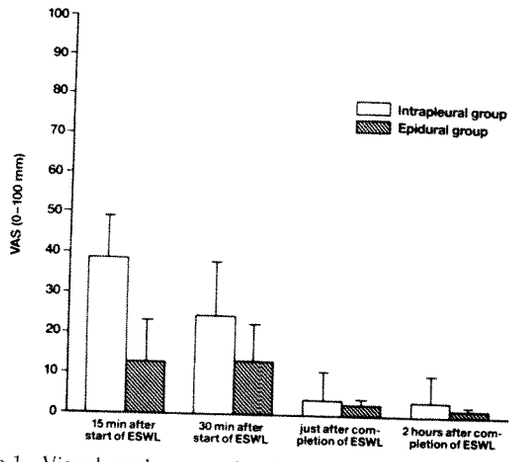

Figure 1. Visual analogue scale of pain 15–30 min after start of ESWL.

Results

There were no significant differences between the groups with regard to age, sex, height, and weight, the numbers of shocks or duration of ESWL (Table 1). All lithotripsy procedures were continued until stones appeared to be adequately fragmented on biplanar x-ray. (One patient needed two ESWL procedures.)

The mean upper level of epidural anesthesia was T 3 (range T 3-6) as evaluated by pinprick. The interpleural technique did not give complete skin anesthesia, but hypesthesia was found from T 2 to T 12 (mean lower level after 20 minutes was T 10).

Pain as evaluated by VAS was significantly greater in the interpleural group ($P < 0.01$ and $P < 0.05$) than in the epidural group 15 (38 ± 4 mm vs 13 ± 6 mm) and 30 min (25 ± 7 mm vs 13 ± 6 mm) after the start of ESWL; however, there were no significant differences in the VAS scores upon completion of ESWL or 2 hr postoperatively (Fig. 1). Significantly more patients required fentanyl in the interpleural than in the epidural group, ($P < 0.01$), while there were no significant differences in the use of diazepam (Table 2). Six patients in each group said they had no discomfort or pain with catheter placement. One patient in the interpleural group complained of severe pain, the other patients in both groups considered the pain minor at catheter placement. Six of the 10 patients in the interpleural group and nine of those

Table 2. Concomitant Medications During ESWL

Interpleural group			Epidural Group		
Patient	Diazepam (mg)	Fentanyl (mg)	Patient	Diazepam (mg)	Fentanyl (mg)
1	—	0.1	1	2.5	0.05
2	—	0.05	2	—	0.1
3	5.0	0.1	3	2.5	—
4	2.5	0.1	4	2.5	0.1
5	2.5	0.1	5	5.0	—
6	2.5	0.15	6	2.5	—
7	2.5	0.05	7	5.0	—
8	5.0	0.15	8	2.5	—
9	5.0	0.2	9	2.5	—
10	5.0	0.25	10	5.0	0.1
Mean	3.75	0.125		3.33	0.088
SD	1.34	0.064		1.25	0.025

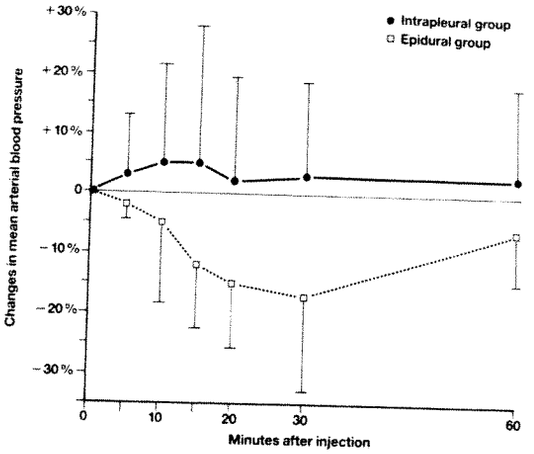

Figure 2. Changes in mean arterial blood pressure during ESWL.

in the epidural group would choose the same anesthesia if ESWL were needed again in the future.

Two patients in the epidural group received ephedrine 40 mg and 30 mg IV. None of the patients in the interpleural group needed ephedrine. In the epidural group, MABP decreased and heart rate increased significantly, whereas there were no significant hemodynamic changes in the interpleural group (Figs. 2 and 3). Respiratory rate remained unchanged in both groups.

Chest x-rays on the first postoperative day did not show any pneumothorax in the interpleural group.

Discussion

The pressure of the shock wave used in ESWL has been described as a sharp pain at the skin combined with deep somatic and visceral discomfort. This was blocked reasonably well with epidural anesthesia in

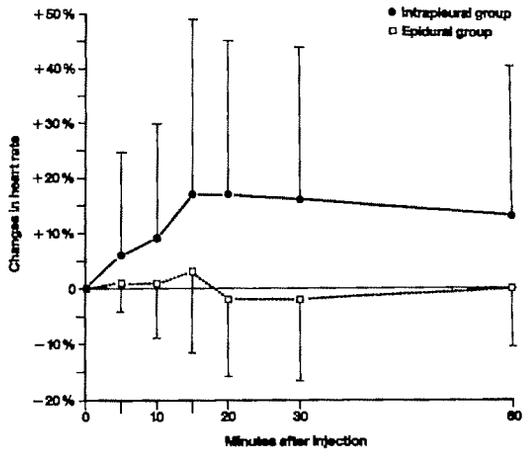

Figure 3. Changes in heart rate during ESWL.

the present study as well as in previous studies (1). In the present study, however, the interpleural anesthesia was less satisfactory. This was probably due to a lesser blockade of cutaneous pain. Similarly, intercostal blocks alone appear to block the deep somatic sensation but not the pain in the skin, while intercostal blocks combined with infiltration of the skin with local anesthetics provides adequate anesthesia (2). Though the exact mechanism by which the interpleural installation of local anesthetics relieves pain is unknown, the most reasonable explanation is a diffusion of the anesthetic solution from the pleural space into the intercostal nerves. Thus, the effect of interpleural anesthesia is similar to that of multiple intercostal blocks. A combination with local infiltration of the skin and interpleural anesthesia should be studied as an alternative to epidural and general anesthesia for patients with an unstable circulation.

The difference in cardiovascular status between the two groups was considerable. In the epidural group MABP decreased and heart rate increased in all patients. In two of the ten patients in the epidural group severe hypotension developed, MABP decreasing to 40–60 mmHg, and heart rate to 42–52, changes severe enough to warrant IV ephedrine and atrophine. In the interpleural group, on the other hand, MABP and heart rate remained stable throughout anesthesia and ESWL.

No patients in this study had evidence of a pneumothorax. We now have experience with interpleural analgesia in 300–400 patients and only two cases of a small pneumothorax not requiring treatment have been observed.

Twenty patients undergoing extracorporeal shock wave lithotripsy were randomly allocated into two groups of 10 patients each. One group received interpleural injections of 20 ml of lidocaine 20 mg/ml and the other group epidural injections of 22 to 25 ml mepivacaine 13 mg/ml. There were no pneumothoraces in the interpleural group and these patients were completely stable hemodynamically while hypotension and increase in heart rate was seen in the epidural group. Pain relief was, however, less satisfactory in the interpleural group and these patients required more supplementary analgesics IV than the patients receiving an epidural injection. We conclude that interpleural injection of local anesthetics is not good enough anesthesia for ESWL.

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Lumbar Root Compression Secondary to Epidural Air

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Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—air injection. COMPLICATIONS, NEUROLOGIC—epidural air.

Lumbar root compression after epidural analgesia resulting in neurologic sequelae has been attributed to peridural hematoma formation. We present a case of lumbar root compression after injection of air into the epidural space.

A 37-year-old woman with stage 4 adenocarcinoma of the cervix with no known epidural involvement was admitted for evaluation of low back and abdominal pain. Medications upon admission included methadone 20 mg every 6 hours, etidronate disodium 200 mg once daily and ibuprofen 600 mg every 6 hours. Physical examination revealed a chronically ill cachectic white female with a well functioning colostomy and a permanent indwelling Foley catheter. The patient weighed 41 kg and had moderate suprapubic and lower lumbosacral tenderness. Initial hematologic, clotting, and chemical profiles were within normal limits.

On the second hospital day the patient was brought to the operating room and a 20-gauge × 90-cm long radiopaque spring wire reinforced epidural catheter (Arrow International Inc., Reading, PA) was inserted at the L3–4 level and advanced 3 cm into the epidural space. One hundred μg fentanyl was injected through the catheter followed by a continuous infusion of bupivicaine 0.125% at 10 ml per hour and fentanyl 100 μg per hour using a constant infusion pump. During the next 12 hours the patient required frequent additional bolus doses of fentanyl 100 μg and 0.25% bupivicaine through the catheter. On the morning of the third hospital day the patient had a T9 sensory level of anesthesia with bilateral motor blockade of the lower extremities. Over the next 4 days the dose of bupivicaine was adjusted to eliminate the motor block. Because of excellent analgesia, it was decided the patient was a candidate for insertion of a permanent epidural catheter. Preoperative laboratory data remained unremarkable. On the eighth hospital day a plastic catheter was uneventfully put into the epidural space at the L2–3 interspace and tunneled subcutaneously along the right lower abdominal wall. The tip of the catheter lay at the L3 level of fluroscopy. A continuous infusion of epidural morphine 0.5 mg/hr, fentanyl 100 μg/hr, and bupivicaine 0.125% 8 ml/hr was initiated with excellent analgesia.

From the 8th through the 11th hospital days, the patient was instructed on preparation of epidural infusions in anticipation of long-term home management. The continuous infusion device was converted to a portable Pancretec 4000+ mini infuser (Pancretec Inc., San Diego, CA).

On the 13th hospital day, a deep venous thrombosis was diagnosed and heparin therapy was initiated. For the next 3 days the ratio between the patient's partial thromboplastin time (PTT) and control PTT ranged from 1.3–1.7, with normal platelet counts. On the 15th hospital day the patient complained of vague lumbar discomfort requiring several epidural bolus injections of fentanyl 200 μg. By the evening of the 16th hospital day multiple epidural injections of narcotic failed to provide analgesia and IV morphine sulfate 3 mg/hr was initiated and the continuous infusion through the epidural catheter was decreased to 5 ml/hr. On the morning of the 17th hospital day the patient complained of worsening back pain with new onset bilateral anterior thigh paresthesias along L2–3. Physical examination confirmed the presence of bilateral hip flexor weakness. Nothing could be aspirated through the catheter. Injection through the epidural catheter was difficult because of marked resistance, and it exacerbated her symptoms. In view of these findings in an anticoagulated patient, an emergency CT scan was performed to rule out an

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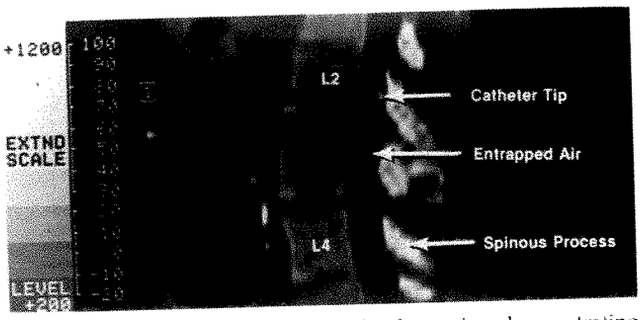

Figure 1. Longitudinal CT scan of lumbar spine demonstrating epidural air.

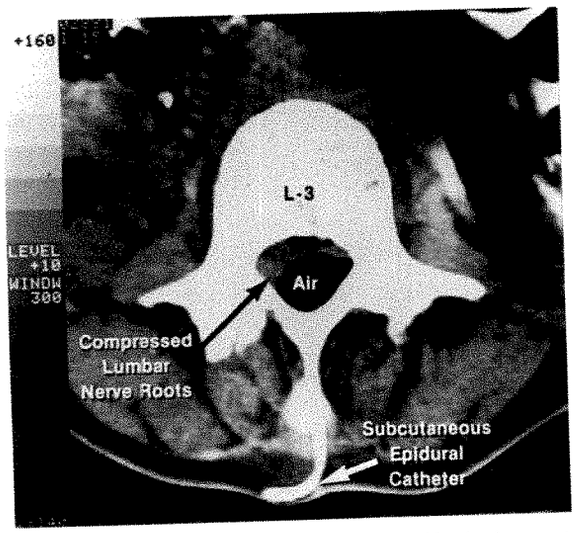

Figure 2. Cross-sectional CT scan at L_3 vertebral body demonstrating significant compression of thecal sac.

acute epidural hematoma. The CT scan revealed entrapped epidural air extending from L1–4 (Fig. 1) with significant compression of the thecal sac at L2–3 (Fig. 2). The epidural catheter tip was at L2. There was no evidence of epidural hematoma.

On questioning, the patient revealed that during self-preparation of her daily epidural solution from hospital days 12 through 17, the patient accidentally injected an unspecified volume of air into each bag. During daily activities the patient repeatedly changed position of the mini infuser and bag system. This allowed the air to gain access to the bag's outlet port and eventually enter the infusion system. Each day the appropriate alarm indicating air in the system was activated. The patient repeatedly silenced the alarm and then purged the air through the intact system into the epidural catheter.

Heparin therapy was discontinued, clotting studies were normalized, and the patient was taken to the operating room for emergency decompression of her epidural space. In the operating room at #17 Tuohy needle was inserted percutaneously into the L1–2 interspace using the loss-of-resistance technique with saline. With the epidural space identified, a plastic catheter was inserted in the caudad direction. Gentle aspiration was performed as the catheter was advanced. At 4–5 cm into the epidural space, a small pocket of positive pressure was encountered and approximately 15 ml of air was aspirated. On removing the air, the patient had immediate relief of her back pain and paresthesias. The temporary catheter was removed and the continuous infusion was resumed through the permanent catheter without resistance or onset of low back pain. Analgesia was subsequently adequate without any permanent neurologic sequelae. The patient died 6 weeks later secondary to metastatic cervical carcinoma.

Discussion

Continuous lumbar epidural infusions are enjoying increased popularity during labor (1) and for management of chronic pain (2,3). As their utilization increases, the number of agents inadvertently injected into the epidural space may also increase (4). Epidural administration of thiopental (5,6), potassium chloride (4,7), magnesium sulfate (8), and particulate matter (9) have been reported. A recent report implicates epidural air introduced using the loss-of-resistance technique as a cause of incomplete analgesia (10).

Spinal cord compression after epidural analgesia is, fortunately, a rare event (11). It is rare for an epidural hematoma and neurologic symptoms to arise if coagulation is normal. However, patients treated with anticoagulants may develop epidural hematomas and possible paraplegia if either an epidural needle or catheter is inserted (12). The incidence of neurologic complications arising from coagulopathies after epidural or subarachnoid catheterization is very low (11). Symptoms of epidural hematoma formation include back pain, lower extremity weakness and urinary or bladder incontinence (13). Any patient developing symptoms consistent with spinal cord compression must have prompt diagnosis and treatment (14).

Over a 14-hour period our patient complained of progressive low back pain with development of bilateral lower extremity weakness and paresthesias. Additionally, attempted injection of narcotic through the epidural catheter produced exacerbation of the patient's back pain. Our first concern was to rule out epidural hematoma because the patient had a partial thromboplastin time ratio of 1.3. The CT finding of epidural air causing lumbar root compression was

unexpected. Immediate decompression resulted in prompt resolution of neurologic symptoms. We are unaware of other reports in the literature describing lumbar root compression secondary to epidurally injected air.

The Pancretec 4000+ mini-infuser consists of a separate pump and 250-ml bag, both of which are conveniently contained in a portable carrying case. Because of the compact nature of the system, multiple position changes of the unit are possible with patient movement. Therefore, strict attention should be paid toward the removal of any air introduced into the infusion bag during its preparation. If air enters the system and the alarm sounds, the system should be disconnected at the epidural catheter and the entrapped air flushed to the atmosphere.

In summary, we present a complication of epidural analgesia administered via a continuous infusion pump, resulting in the epidural injection of air with lumbar root compression. Early diagnosis and treatment with percutaneous epidural decompression prevented any permanent sequelae. Findings suggestive of a large volume of epidural air may include increased resistance to infusion, escalating analgesic requirement, and progressive back pain exacerbated with epidural injection of analgesic.

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Tension Pneumothorax during Dental Anesthesia

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Key Words: ANESTHESIA—maxillofacial. SURGERY—dental. LUNGS—pneumothorax.

Subcutaneous emphysema of the face or neck which may extend into the mediastinum can complicate the use of high-speed air-turbine dental drills (1–5) or dental extractions (1). Pneumopericardium with subcutaneous emphysema has also occurred after maxillary surgery (6). Pneumopericardium, where air may have forced its way through a tear in the mucous membrane of the upper respiratory passages, has been reported to have occurred during a high-speed ride on a motorcycle (7).

This case report describes the development of subcutaneous emphysema of the face, neck, and chest wall with mediastinal emphysema and tension pneumothorax that occurred during conservative dentistry using an air-turbine dental drill.

Case Report

A 4-year-old boy weighing 15 kg with symptomatic homozygous B thalassemia was scheduled for dental fillings and restoration under general anesthesia. The patient's anemia was managed with three weekly packed red cell transfusions of 200 ml and desferoxamine 500 mg IV three times a week. He had hepatosplenomegaly and the liver edge was palpable 4 cm below the costal margin in the right hypochondrium. The hemoglobin level on the day of the operation was 9.8 g/dl. Anesthesia was induced with thiopental 100 mg IV and tracheal intubation was facilitated with pancuronium 1 mg. Induction was smooth and intubation easy. Maintenance of anesthesia was with nitrous oxide (N_2O) and oxygen; pancuronium supplemented with fentanyl, and intermittent positive pressure ventilation (IPPV).

After 2 hours of surgery, a swelling of the soft palate was noticed. There was no crepitus. The surgeon noted that the gingival tissue appeared to be friable and tended to bleed easily. In the absence of other signs, surgery was continued and the lesion observed. One hour later the peak inflation pressure increased sharply from 20 to 40 cm H_2O. Auscultation of the chest revealed extensive bilateral wheezes. Bradycardia and hypotension developed rapidly and after 2 minutes the blood pressure was no longer recordable. Abdominal distension that was tympanic to percussion was seen and there was extensive crepitus over the neck and chest wall. The liver edge was palpable 3 cm below the level of the umbilicus and it was suspected that the liver had been displaced by increased pressure in the right hemithorax as a result of a tension pneumothorax. A 20-gauge cannula was introduced into the right pleural space in the mid-axillary line in the fourth intercostal space with dramatic results. The heart rate increased from 30 to 150 beats/minute, the blood pressure was recordable at 80/60 mm Hg, and a wheeze was no longer audible. A chest tube was inserted into the right pleural cavity and a chest x-ray was taken immediately afterward. The chest x-ray showed emphysema of the neck, chest wall, and mediastinum, as well as a right-sided pneumothorax. In the neck and chest wall, air had dissected along tissue planes into the fascial sheaths of the sternocleidomastoid and pectoralis muscles.

With the chest drain in place, dental surgery was resumed under N_2O anesthesia and when the procedure was completed, patient was transferred to the intensive care where he was weaned off IPPV 6 hours later. The patient made an uneventful recovery and was discharged on the third postoperative day.

Discussion

This case report is another example of an association between high-speed air-turbine dental drills and tissue emphysema. The turbine is driven by compressed air at 30 psi at about 20,000 rpm. A small jet

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of air and water is directed to the drill tip to cool the point. In the older models this jet of air was bled from the turbine, (5) whereas in the newer models air is led to the head of the handpiece by a separate conduit (supplied at 20 psi). Air syringes used to dry dental caries generate a pressure of 20–25 psi and may cause subcutaneous emphysema (2). It has been shown experimentally that death can occur when air is forced into the root canals of dogs (2).

Air enters tissue planes through tears in the oral mucosa or is forced between tooth and gum (1). The subsequent swelling of the floor of the mouth has been mistaken for angioneurotic edema (8), and could pose a differential diagnostic problem: hematoma, abscess, or edema.

In this case it is difficult to associate the hemoglobinopathy with the development of tissue emphysema. However, the surgeon noted that the tissue was friable and therefore it could be postulated that the tissues admitted air into the tissue planes more readily. The possibility of pulmonary barotrauma from an intra-anesthetic overpressure accident cannot be ruled out. However, considering that the swelling of the soft palate was noted an hour before the acute cardiovascular collapse occurred, it is likely that air tracked along the fascial planes of the sternocleidomastoid muscle to the mediastinum when a rupture of the mediastinal pleura resulted in pneumothorax. The ability of N_2O to diffuse into body cavities and the use of IPPV may have contributed to the development of tension. There is experimental evidence to show that the pleura is most likely to rupture at two sites with mediastinal emphysema: 1) an area above the root of the left lung and, 2) a fold of mediastinal pleura that lies against the pericardium (9). Although a wheeze often suggests bronchospasm, it can also occur with a pneumothorax (10), probably as a result of distortion of the bronchi.

When subcutaneous emphysema of the neck or face is present, it is possible that emphysema of the mediastinum (and possibly pneumothorax) has also occurred and therefore warrants discontinuation of N_2O and interruption of surgery so that an x-ray of the chest may be taken to assess the extent of "pneumatic dissection." When possible, surgery should be discontinued because the progression of subcutaneous emphysema to mediastinal emphysema bears potential for the dangerous complication of a tension pneumothorax.

When the dental drill is used, a rubber dam usually prevents the jet of air from playing on soft tissue (4), although in this case tissue emphysema occurred in spite of the rubber dam. Clear plastic drapes allow observation of the patient intraoperatively (2). The occurrence of mediastinal emphysema when there is severe periodontal disease probably justifies prophylactic antibiotic therapy because mediastinitis leading to death has occurred after faciomaxillary surgery (11).

We are grateful to M. Almeida and C. Parzanese for technical assistance and Dr. J.C. Bevan for criticism in the preparation of this manuscript.

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Perioperative Cardiovascular Collapse in a Patient Previously Treated with Doxorubicin

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Doxorubicin (Adriamycin), an intravenously administered cancer chemotherapeutic agent with a broad spectrum of activity, is usually well tolerated (1). Unfortunately, repetitive administration of doxorubicin may be associated with a dose-dependent irreversible cardiomyopathy (2). We are unaware of any report on interaction between anesthetics and doxorubicin.

We report the case of a patient who developed an acute intraoperative left ventricular failure 2 months after the cessation of treatment with doxorubicin.

Case Report

A 44-year-old woman was admitted for an elective bilateral oophorectomy. A left mastectomy was carried out for an invasive adenocarcinoma. One year later a relapse necessitated a right mastectomy. Chemotherapy with doxorubicin was started a month later, after the appearance of bone metastases. In 1 year the patient had received a total dose of 460 mg/m^2 of doxorubicin. The treatment was well tolerated and the clinical response was favorable, with significant and progressive disappearance of x-ray bone lesions. However, the treatment was discontinued because signs of moderate congestive heart failure appeared, consisting of mild dyspnea associated with a decrease in left ventricular ejection fraction evaluated by radionuclide angiocardiography from 67% (before the introduction of chemotherapy) to 56%. A bilateral oophorectomy was planned to prolong the remission.

The patient weighed 74 kg and was 171 cm tall. She complained of a slight dyspnea (stage II according to the NYHA) but of neither orthopnea nor paroxysmal noctural dyspnea. She was found to be in well-compensated moderate congestive heart failure. No cardiotonic drugs were considered necessary. There was no jugular turgescence, hepatomegaly, or ankle edema. Cardiopulmonary auscultation was unremarkable. Blood pressure was 130/80 mm Hg; heart rate was 80 beats/min with a regular sinus rhythm. Chest x-ray was also unremarkable. ECG was in the normal range (PQ and QRS intervals 0.16 and 0.09 seconds; axis + 10°, no evidence of left ventricular hypertrophy) and comparable with previous ECGs. Blood gas analysis and electrolyte levels were all within normal limits.

The patient was premedicated with atropine 0.5 mg IM and midazolam 5 mg IM. Before induction, blood pressure was 120/80 mm Hg and central venous pressure 10 cm H^2O (through an antecubital catheter, the tip of which lay in the superior vena cava by x-ray). Anesthesia was induced with etomidate, 15 mg IV. Pancuronium, 7 mg IV, was used to facilitate tracheal intubation. Analgesia was assured by fentanyl, 200 μg IV, given in two separate doses. Anesthesia was maintained with halothane (0.5–0.7%), nitrous oxide (66%), and oxygen (33%). Ventilation was controlled with a tidal volume of 700 ml at a rate of 12 breaths/min. The anesthesia and the operative procedure went smoothly. Ninety minutes after induction, the arterial blood pressure abruptly decreased to 70/40 mm Hg. The heart rate remained unchanged, with a normal sinus rhythm, and the central venous pressure remained stable at 12 cm H^2O. Halothane and nitrous oxide were immediately stopped and the patient was ventilated with 100% oxygen. On physical examination neither rash nor skin turgescence were noted.

Trendelenburg position, calcium chloride (100 mg IV), and ephedrine (15 mg IV) associated with an increased rate of fluid administration (500 ml colloïde in 15 minutes) had no effect on blood pressure. Dopamine, 400 μg/min, and dobutamine, 500 μg/min, increased systolic blood pressure to 100 mm Hg. Blood loss in the operative field was negligible. The operative procedure was promply terminated and the patient transferred to the intensive care unit. At this time a protodiastolic gallop and stasis rales were audible. A pulmonary arterial catheter inserted at that time showed right atrial pressure to be 8 mm Hg,

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pulmonary artery pressure 30/20 mm Hg, pulmonary wedge pressure 18 mmHg, and cardiac output 1.8 ml^{-2}. Systemic blood pressure was 100/70 mm Hg. The patient was being mechanically ventilated without PEEP. A diagnosis of acute left ventricular failure was made.

Bidimensional echocardiography was unremarkable, except for an anteroseptal hypokinesia. There was no increase in plasma levels of cardiac enzyme (CK,CK-MB). Electrocardiographic recordings showed no changes suggestive of ischemia. Blood cultures and an extensive search for infection were negative. After treatment with inotropic agents, peripheral vasodilatators and diuretics the patient was discharged from the intensive care unit 5 days later without inotropic drugs with a pulmonary wedge pressure of 11 mm Hg and a cardiac output of 3.4 ml^{-2}. Subsequent course was cardiovascularly uneventful.

Discussion

The intra-operative appearance of a rapid decrease in systemic blood pressure in a previously normotensive patient can be due to many causes. The absence of significant blood loss and the maintenance of a normal central venous pressure argued, in the present case, against acute hypovolemia. A septic process was unlikely in face of a low cardiac output, the absence of an infection focus despite extensive search, and an unremarkable WBC count without increased band forms. Bidimensional echocardiography excluded valvular or pericardic pathology. Pulmonary arterial hemodynamic values made pulmonary embolus unlikely. The absence of either increases in plasma levels of cardiac enzymes or ECG changes argued against an ischemic injury. The absence of rash or skin turgescence and the time between the intravenous administration of anesthetic drugs and the appearance of the acute hypotension (90 minutes) make an anaphylactoid reaction unlikely. The diagnosis, therefore, was acute left ventricular failure, probably due to a latent cardiomyopathy secondary to previous treatment with doxorubicin.

Approximately one third of patients given high doses of doxorubicin develop symptomatic congestive heart failure (3). The appearance of a cardiomyopathy is rare with doses under 200 mg/m^2 of doxorubicin and unpredictable with doses between 200 and 550 mg/m^2, but over this value the incidence of cardiomyopathy increases (4). Bristow et al. (5) have shown that the effects of doxorubicin on cardiac myocytes and myofibrillar dropout, consisting of vacuolization of the sarcoplasmic reticulum and complete loss of myofibrils, appear long before the effects on cardiac function can be detected. Even with doses of less than 200 mg/m^2, cellular lesions can be seen with endomyocardial biopsy. The same authors also found that the late appearance of clinical symptoms of heart failure despite advanced myocardial damage following the administration of doxorubicin to be due to a hyperactive sympathetic system. Moreover, prolonged hyperadrenergic stimulation progressively decreases the number of cardiac β-adrenergic receptors to the point where no amount of catecholamine can mediate a satisfactory response in the heart (6).

In our case, one wonders why 90 minutes elapsed before severe left ventricular failure developed. There is no definitive explanation. However, in our patient near normal pre-operative heart function was, according to the hypothesis of Bristow et al. (5), maintained by a hyperactive sympathetic system. Moreover, the surgical procedure, a stressful situation, and the administration of anesthetic drugs, most of which possess a negative inotropic effect, created a supplementary burden known to stimulate the sympathetic system. In this clinical context, prolonged hyperstimulation of the adrenergic system (doxorubicin cardiotoxicity) decreases the number of β-adrenergic receptors (6). We assume that the combination of all these factors progressively exhausted the already limited adrenergic system to a point where maintenance of normal heart function was impossible, thus explaining the time lapse between induction of general anesthesia and left ventricular failure. The fact of the absence of any increase in heart rate despite a decrease cardiac output as well as the type of failure (acute and transient) favors this possibility.

The physiopathologic features associated with doxorubicin cardiomyopathy makes safe use of most general anesthetics difficult, even in a patient with near normal heart function, as in our case. We do not, however, recommend that patients previously treated with doxorubicin be given halothane, the negative inotropic effect of which is proportionnal to the dose administered (7), an effect normally compensated by the adrenergic system (8).

The present case suggests that the anesthesiologist should be careful in choosing the type and technique of anesthesia in patients who have previously undergone anthracyclines treatment because of the danger of latent cardiomyopathy that can decompensate during general anesthesia.

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Letters to Editor

Flapper Valve Malfunction

Note: This response to the letter on Eisenkraft et al. entitled "Flapper Valve Malfunction" (see p. 1132) was omitted inadvertently from last month's issue.

To the Editor:

I would like to point out that both patients were adequately ventilated. "Ventilation was judged adequate by clinical parameter, end tidal CO_2 level using mass spectrometry, and repeated blood gas analyses" (1). The fresh gas flow had to be increased from 3.0 L/M to 5.0 L/M to compensate for the gas leak and correct the problem, but ventilation was never inadequate.

I agree that the malfunctioning flapper valve described in the report leading to the gas leak is the ventilator relief valve.

There was no reason or plan to hyperventilate either of the two patients. In case 1, before adjusting the minute volume guided by the patient's weight, the ventilator was set to deliver a tidal volume of 900 ml at a rate of 11 breaths/min. Even with that large minute volume, "it was immediately noticed that the chest expansion was inadequate and breath sounds were equal but weak" (1), and a gas leak was immediately suspected.

The location of the gas leak was suspected early on. During case 1, "on manual ventilation, the chest expansion was adequate and breath sounds were equal and well heard" (1), and hypoventilation occurred only when the patient was mechanically ventilated. A gas leak, not in the anesthesia machine but in the ventilator, was suspected. We did not notice distension of the scavenging reservoir bag; most probably the screw valve on the interface was completely open and the excess gasses vented into the room. The malfunction of the stem of the flapper valve was found only by disassembling the parts of the valve and using soap bubbles.

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Reference

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Generalized Convulsions Following Regional Anesthesia: A Pertinent Lesson

To the Editor:

A 22-year old male (approx 65 kg) was admitted at 11:55 a.m. for repair of the left ulnar nerve following a machete injury. Though he claimed he had not eaten or drunk anything since 3–4 a.m., he was under the influence of alcohol. His pulse rate was regular at 80 bpm, and blood pressure was 95/70 mm Hg; hemoglobin was 10.5 gm%. One month previously he had undergone an uneventful laparotomy for a stabbed abdomen; otherwise he was healthy.

At 13:15 an intravenous infusion of Plasmalite L (Na-131, K-5, C1 107, lactate 29 mmoles per liter) was commenced and at 13:30 a supraclavicular brachial plexus block was performed using the technique described by Macintosh and Mushin (1) with a mixture of 1.5 mg/kg (20 ml) bupivacaine 0.5% (20 ml) and 1.5 mg/kg lidocaine 1% (10 ml). At 13:45 the patient developed what appeared to be generalized convulsions. However, he was breathing adequately, his color was good, pulse was 90 and regular and the systolic blood pressure was 140 mm Hg. Because of these clinical findings and the 15 minutes between injection and onset of the convulsions, we did not consider this reaction to be the result of a toxic reaction to the local anesthetic agents (slow absorption could have delayed the onset of the toxic blood local anesthetic peak, but this is unusual in our clinical experience). The initial treatment therefore consisted only of high flow oxygenation given via a face mask. Two other possibilities were considered: the patient had undiagnosed epilepsy, or had a hypoglycemic coma. Though he did not show all the classical signs of an epileptic convulsion such as incontinence and tongue biting, thiopental 30 mg was injected slowly iv but with no diminution in the convulsions.

Because of the history of recent excessive alcohol intake, 60 ml of 50% dextrose was injected slowly iv 3–4 minutes after the onset of convulsions. A blood sample taken after the dextrose solution had been injected revealed a blood sugar of 2.5 mmol/liter, normal (fasting) levels being 3,3–6,6 mmol/liter. More glucose was given as 40 ml of 50% dextrose in 1 litre of Plasmalite L. The blood sugar 1 hour

later was 9.7 mmol/liter and the plasma electrolyte levels were normal. His convulsions subsided over 10 minutes following the intravenous glucose injection and he made an uneventful recovery. His ulnar nerve was repaired under the regional block.

We wish to call attention to this case for three reasons. First, excessive alcohol can cause hypoglycemia and therefore measurements of blood glucose levels in cases such as this should be considered. Second, the prescribed treatment of toxic reactions to local anesthetics, i.e., paralysing and ventilating, without having given glucose, might have been extremely dangerous in this patient. Third, had this patient had a general anesthetic, the symptoms of hypoglycemia would have been masked with possible ensuing brain damage.

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1. Macintosh RR, Mushin WS. Local Anaesthesia: Brachial Plexus, 4th Ed. Oxford: Blackwell, 1967 (1st ed. 1943).

Hypothermia, Myocardial Protection, and Cold Agglutinin Disease

To the Editor:

Park and Weiss (1) are quite correct in stating that none of the reported techniques used to manage patients with cold agglutinin disease during open heart surgery is superior to the rest. The importance of determining the thermal amplitude of the cold agglutinin, however, was not sufficiently emphasized in their management plan. This is particularly relevant if preoperative plamapheresis is performed to reduce antibody titres. Unless measures are taken to maintain the patients blood above the thermal amplitude during open heart surgery, agglutination may be initiated. Additionally, during cardiopulmonary bypass erroneous hematological indices may be recorded if blood samples are allowed to cool below the thermal range either before or during measurement, e.g. agglutination causes a falsely low hematocrit.

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1. Park JV, Weiss CI. Cardiopulmonary bypass and myocardial protection; management problems in cardiac surgical patients with cold agglutinin disease. Anesth Analg 1988;67—8.

A Tidy Adjunct to Oropharyngeal Airways

To the Editor:

I would like to share a simple technique with you for daily anesthesia management. When I set up for a case, I insert a tongue depressor into the side slit of an airway (Berman type) and engage them together as shown in Fig. 1. This

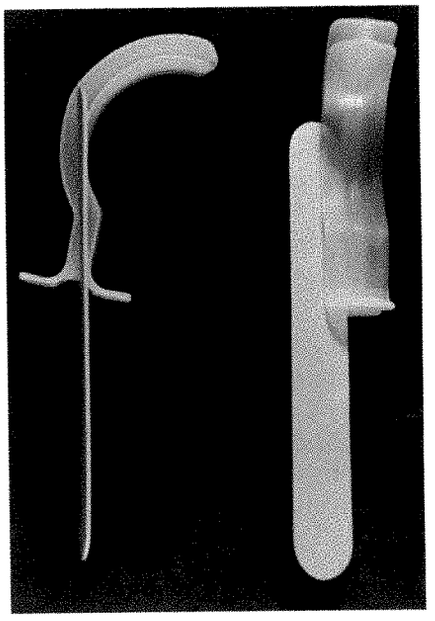

Figure 1. Oropharyngeal airway with tongue depressor attached.

will prevent searching for a tongue depressor when the insertion of an oropharyngeal airway is necessary.

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Book Reviews

Obstetric Anesthesia

Sivam Ramanathan, MD. Philadelphia: Lea and Febiger, 1988, 420 pp, $45.00.

Although a growing number of multi-authored volumes relating to obstetric anesthesia have been appearing in recent years, this text is unusual in being the product of one physician's practice and experience. The advantage of this is a uniformity of style and viewpoint that makes for easy reading. The drawback is a single-mindedness of approach to a field which has become more complex as it has been increasingly involved in the wider areas of perinatal medicine and neonatology. The book serves as a useful text and basic manual for the administration of obstetric anesthesia, without claiming to be a definitive source of reference.

Section I on normal pregnancy is concise, makes good use of figures and illustrations, and lives up to the author's claim to avoid "controversy and court safety" in the choice of anesthetic agents and techniques. The chapters on high-risk pregnancy are informative and exhaustive, including sections on obesity, and a timely one on drug abuse. Though very sound views are expressed, this is the area where it might be more interesting for the reader to consider alternative or varied forms of therapy, rather than one personal choice.

Part III, which involves chapters on fetal monitoring, newborn resuscitation, prematurity and neonatal emergencies, is well-planned and useful, again making very effective use of illustrations. As a minor criticism, better proofreading would have been beneficial. All in all, this very comprehensive effort is a welcome addition to the available texts.

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Foundations of Obstetric Anesthesia

Barbara S. Morgan, London: Farrand Press, 1987, 314 pp, $39.50.

The nineteen chapters in *Review of Foundations of Obstetric Anesthesia* include contributions from authorities in the fields of anesthesiology, obstetrics and pediatrics. The text successfully provides a basic foundation of knowledge for all health providers involved with perinatal care, is well-written, and easily read.

The first chapter provides an interesting historical background on the development of regional analgesia in obstetrics. The chapters entitled Anatomy and Physiology of Epidural Block, Complications of Epidural Block, Aspiration Pneumonitis, Placental Transfer, and Hemostasis in Pregnancy are additional strengths of the book. The section on methods to reduce anesthetic-related deaths within the chapter on mortality and anesthesia is timely and provides some excellent recommendations.

The text contains several inaccuracies and is incomplete in many areas. Numerous times the book claims that epidural anesthesia is associated with a higher rate of forceps extraction implying that there is a causal relationship between epidural block and subsequent forcep deliveries, something that has never been demonstrated. Conversely one chapter questions the causal relationship and offers several possible explanations for the association. Another section claims that a larger episiotomy as well as the use of forceps may be the result of an epidural block for labor and delivery. The author suggests that the patient should weigh the above risks versus a shorter and more painful labor. Dr. Morgan obviously feels quite strongly that patients in normal labor should be discouraged from requesting epidural analgesia for she writes, "It is a physiological process that should not require invasive medical procedures." She further states, "The indiscriminate use of epidural block on the insistence of mothers in normal labor may be minimized if the mother is reassured that the pain will be contained, with simpler analgesics for the remaining short period of labor." Along with comfort this reviewer believes there are other advantages to epidural anesthesia such as decreased maternal hyperventilation, decreased circulating maternal catecholamines and a more controlled delivery. Accordingly this reviewer suggests that a more comfortable and safe alternative for an potentially painful physiologic process such as normal childbirth should not be discouraged.

Another chapter mentions that epidural anesthesia may cause babies to appear "floppy but alert", then concedes that such neurological manifestations are unimportant. Recent work does not indicate that epidural anesthesia is associated with a decrease in neurobehavioral scores, if

administered properly, regardless of the agent used. There is no real discussion on the use of epidural narcotics for post-operative pain relief. The chapter on pregnancy and cardiovascular disease is cursory and provides few guidelines for the practitioner. The discussion of pre-eclampsia and other coexisting diseases such as diabetes is brief to non-existent.

The book provides a substantial amount of useful information on the basics of obstetrical anesthesia in a well-written text. It is not a complete resource for a clinical anesthesiologist presented with a high risk parturient. Recommending this book to obstetricians, student anesthetists and residents is qualified in that the text contains some misinformation and an unusual philosophical bias.

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Fifty Years: The Australian Society of Anaesthetists 1934-1984

Gwen Wilson. Edgecliff, New South Wales. Australian Society of Anaesthetists, 1987, 502 pp.

When the Australian Society of Anaesthetists decided to have written a history of the first fifty years of its existence, Dr. Gwen Wilson, a well-known and distinguished historian who had been intimately involved in many of the events of that era and with most of the individuals who had been responsible for the development of the society, was selected to write the history. The result is a remarkable chronicle based not only upon her first-hand knowledge but upon exhaustive research. Dr. Wilson obtained her Diploma in Anaesthetics in Sydney in 1945 and was a foundation member of the Faculty of Anaesthetists and fellow in 1954.

The book is not easy reading. I found particularly bothersome the many abbreviations such as AGM, BMA, AAGBI, ASA as well as the abbreviations for the Australian states such as NSW, Qld, V, SA and Tas (although a very complete list of abbreviations is included on page 12). It is also made difficult by the fact that a great deal of the text consists of quotes from correspondence between the members and minutes of the various meetings. Even though such may be good history, it makes for dull reading.

The early years of the society were difficult indeed. When one considers the size of the Commonwealth of Australia, nearly three million square miles (approximately the size of the U.S.) it is easy to contemplate the great difficulties in organizing a medical specialty group which began with fewer than 100 members! Distances were vast, transportation and communications were not as advanced as they are now, and it must have taken major efforts to bring the founding group together. There was also great rivalry about the location of the national headquarters since any place selected would be inconvenient or inaccessible for many. We must remember also that the bulk of anaesthetics in the early days were administered, not by nurse anaesthetists, as in the U.S., but by general practitioners who were in many cases family doctors and referring physicians.

Credit is given the great assistance of the McMechans and by Ralph Waters in the early attempts at organizing anaesthesiology in Australia. In addition to superb input from Britain, many Americans are mentioned as "Official U.S.A. Visitors" including (among others) Ron Stephen, Barrie Fairley, Jim Eckenhoff, Manny Papper, Ron Katz, E. Cohen, Jack Downes, Dick Kitz and Lucien Morris. But these are mentioned under "Years of Fulfillment 1962–84" which was written as a postscript by Dr. Ben Barry at Dr. Wilson's request.

The book is neatly divided into sections which describe the foundation and founders, the first five years, the period of reconstruction after World War II, the trials and arguments involving the establishment of a national health service, the foundation of the Faculty of Anaesthetists and relationships with the BMA and the certifying groups.

The name of Dr. Geoffrey Kaye, first secretary of the Australian Society of Anaesthetists appears on almost every page of the first five chapters of the book, and rightly so. A man of great energy and enthusiasm, Kaye was probably the greatest single organizing force in the Society. He corresponded with his peers all over the world, founded the Newsletter, encouraged the initiation of the Journal, and at one point even provided at his own expense a house for the Society's headquarters (Mathoura Road). Unfortunately, when he died in 1987 at the age of 84 some of his efforts were still unappreciated by the membership for reasons that are not quite clear to this reviewer. However, one of his great dreams, the Museum that bears his name, will continue to honor his memory.

This is a superb book, but one that may have limited interest for most anesthesiologists. It is to be particularly recommended, however, to those who have an interest in the history of anaesthesiology on a world-wide basis and particularly those who have visited or have close ties to Australia.

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Obstetric Anesthesia: The Complicated Patient (Second Ed)

Francis M. James III, A. Scott Wheeler, David M. Dewan, eds. Philadelphia: F. A. Davis Co., 1988, 577 pp, $79.00.

The first edition of *Obstetric Anesthesia: The Complicated Patient* has served as an invaluable handbook for practicing anesthesiologist for the past six years. Even those who infrequently cover the obstetric suite are called upon occasionally to care for a pregnant patient with coexisting medical conditions, ranging from von Willebrand's disease to mitral stenosis or myasthenia gravis. The first edition

offered well referenced, practical advice on how to devise and implement an appropriate anesthetic plan for labor and delivery or non-obstetric surgery, no matter how complex the circumstances. The advent of new pharmacologic agents in medical therapy and anesthetic innovations such as the use of epidural narcotics has made the need for an updated version of James' and Wheeler's book apparent.

This new edition, under the added co-editorship for Dr. David Dewan, ably fulfills its task of updating the original version, and contains many references to recent literature. A new type face and two-column format are welcome changes that improve the book's readability. The book has been expanded to include a number of new chapters that serve to make it a much more comprehensive textbook of obstetric anesthesiology and perinatology.

The first five chapters contain almost entirely new material, and include thorough discussions of the physiologic changes of pregnancy, the physiology of the fetus and placenta, and the effects of medications on the fetus and neonate. A chapter on fetal assessment has been revised and now includes detailed photographs of ultrasound scans, and a section on the use of Doppler flow studies to identify uteroplacental insufficiency. An excellent chapter on maternal and fetal morbidity and mortality provides a concise, thorough review of complications related both to anesthesia and obstetrics and offers a valid critique of the Scanlon study, which for so long was held back the use of lidocaine in obstetric anesthesia. Another useful new chapter discusses the anesthetic implications of problems that may arise in early pregnancy, such as ectopic and abdominal pregnancy, trophoblastic disease, abortion, and incompetent cervix.

A newly added second section of the book attempts to present a review of anesthesia for the uncomplicated patient. This is perhaps the least successful portion of the volume. The chapter on anesthesia for routine births provides a sound general overview, but does not contain enough detail to serve as a guide to the beginner. Another chapter on anesthetic complications reiterates much of the material that was already presented in the discussion of morbidity and mortality.

The remainder of the book contains updated chapters on maternal illness by system, specific fetal problems such as preterm delivery and multiple gestation, and special problems including pregnancy-induced hypertension and anesthesia for non-obstetric surgery. These areas were a major strength in the first edition and, if anything, are better in the second. Chapters are clearly organized with subheadings which quickly direct the reader to the topic of choice, whether routine or rare. The chapter on neurologic disease is essentially unchanged from the first edition; the one on cardiac disease has been revised and updated (although the discussion of mitral valve prolapse offers more advice about what not to do than what is to be done). There is a new and substantially helpful chapter on orthopedic disease that covers common concerns such as backache and scoliosis and also offers thorough reviews of less common subjects such as neural tube defects. Discussion of the febrile parturient has been expanded to include the management of AIDS, and cocaine abuse receives more thorough treatment than was warranted in 1982. Finally, an entirely new chapter on management of the pregnant patient who has suffered major trauma does a creditable job of emphasizing how the physiologic changes of pregnancy confer increased risk, especially of hypoxemia, while they complicate physical assessment and estimation of blood loss.

The second edition of *Obstetric Anesthesia: The Complicated Patient* continues to be a superbly practical yet comprehensive volume that merits space on the bookshelves of any obstetric anesthesia service. As Dr. Gertie Marx points out in her introduction, many pregnant patients are neither young nor healthy, but any of them may require our care at any time.

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Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Dundee JW, Wyant GM. Intravenous Anaesthesia, Churchill Livingstone, New York, 1988, 358 pp, $89.00.

Lenz G, Kottler B, Schorer R, Spoerel WE. Pocket Manual of Anesthesia, BC Decker, Inc. Philadelphia, 1988, 318 pp, $18.50.

Lynch NT, Vasudevan SV. Persistent Pain: Psychosocial Assessment and Intervention, Kluwer Academia Publishers, Boston, 1988, 208 pp.

Mazala M. Pediatric Anesthesia and Emergency Reference, Mazala Medical Software, Cherry Hill, NJ, 1988, one disk.

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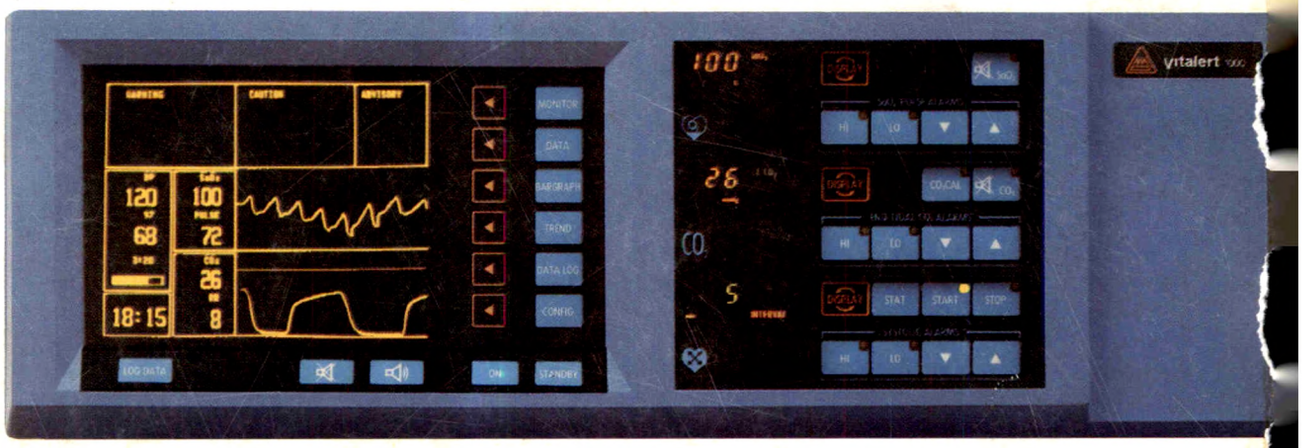

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Information available on the display screen includes: Structured Alarm Messages, Waveforms, Digital Data, Bargraphs, Trends and a Tabular Data Log.

Vitalert™ 1000 can be configured for pulse oximetry, capnography and noninvasive blood pressure measurement.

Designed to functionally integrate with the Narkomed 2A, Narkomed 2B, ***or operate on its own,*** Vitalert™ 1000 provides the operator with the advantages of a ***truly*** integrated system, including

- structured alarm strategy
- central alarm display
- central alarm silencing
- custom configurable default values
- comprehensive data display
- auto-enabled data logging
- storage and hard copy documentation capabilit
- electronic transfer of information
- generic serial port for customized programming

Vital information with t
central **Alert** philosophy.

For more information contact North American Drager or your dealer.

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